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Original Articles

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PRESENTATION OF PAUL EHRLICH MEMENTOS

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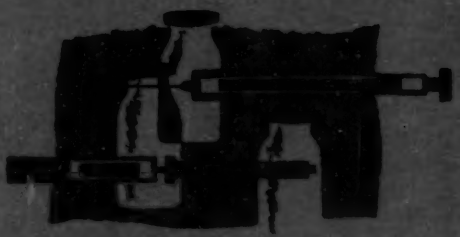

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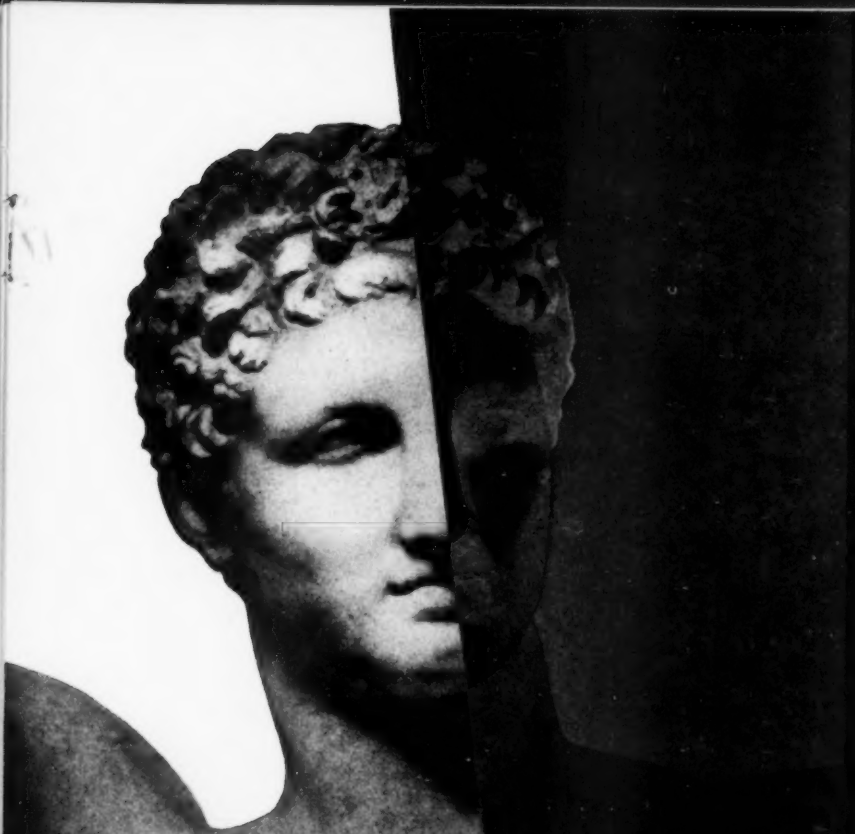

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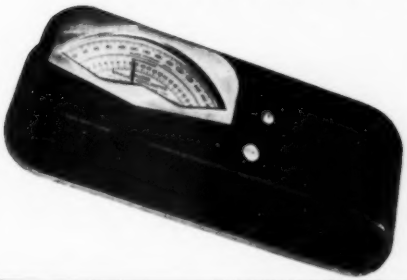

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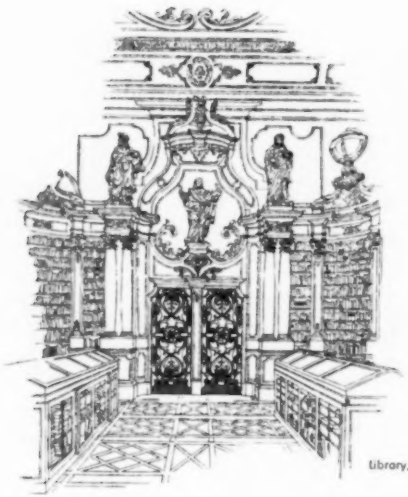

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CONTENTS

Diet and Lipotrophic Agents in Atherosclerosis . . . 279
John W. Gofman

The Importance of Cardiac Arrhythmias 294
Louis N. Katz

Present State of Knowledge Concerning Pathogenesis and Treatment of Rheumatic Fever 307
Maclyn McCarty

The Epidemiology and Prevention of Rheumatic Fever 321
Charles H. Rammelkamp, Lewis W. Wannamaker and Floyd W. Denny

Presentation of Paul Ehrlich Mementos: *Hans W. Scherin* 335

Paul Ehrlich—As Man and Scientist: *Selman A. Waksman* 336

Paul Ehrlich and Modern Chemotherapy: *Perrin H. Long* 344

Section on Microbiology:

Induction of Penicillin Resistance by Transfusion 346
Rollin D. Hotchkiss

Purification and Analysis of the Transforming Principle of Hemophilus Influenzae, *Stephen Zamenhof* 349

Transformation Reactions in Hemophilus Influenzae . . . 350
Hattie E. Alexander

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 28, NO. 5 MAY 1952

DIET AND LIPOTROPHIC AGENTS IN ATHEROSCLEROSIS*

JOHN W. GOFMAN

Associate Professor of Medical Physics, University of California, Berkeley

A RATIONAL approach to the management of atherosclerosis and its clinical sequelae can best be made by a delineation of those aspects of the disease which may be accessible. Two major features are striking about atheroma formation: (a) the definitely focal character of the lesions; and (b) the abnormality in serum lipids associated with the development of the disease.

Unfortunately our knowledge of the nature of the factors operative in producing the focal feature of atheroma formation is primitive. Until there is more light shed on this highly important problem, there is little hope of a therapeutic approach via the control of such factors. However, the discouraging state of our information concerning the basis for variable local vascular susceptibility to lesion formation should in no way be allowed to prevent a vigorous effort to cope with the general factors, namely, disturbed lipid metabolism and transport, which partici-

* Presented at the 24th Graduate Fortnight of The New York Academy of Medicine, October 9, 1951. From the Donner Laboratory of Medical Physics and the Radiation Laboratory, Department of Physics, University of California, Berkeley, California.
The research upon which this talk is based was supported in part by the United States Public Health Service, the Atomic Energy Commission, and the Lederle Laboratories Division of the American Cyanamid Company.

pate in the evolution of atherosclerosis. Whereas many investigators may disagree, the most plausible concept of the pathogenesis of this disease is that certain circulating lipids are deposited and retained in susceptible focal areas to produce atherosclerotic lesions. The various histopathologic features characterizing the lesions may then represent the result of secondary processes, including possibly regressive changes, in the evolution of the mature disease. It is with the general factor, the lipid factor, that the present considerations are concerned.

The Serum Lipid Factor in Atherosclerosis

In several publications,[1-5] a group of us have described several lipoproteins in the serum of humans, certain of which lipoproteins are associated with atherosclerosis.* The developing studies of these lipoproteins now allow some systematization of lipoprotein interrelationships. Our present concepts of such interrelationships will undoubtedly require modification and extension, but still are useful for orientation and the planning of further studies.

The lipoproteins to be found in human serum are characterized in general by having a density lower than that of such serum proteins as the albumins and globulins. Further the lipoproteins range in density from those as high as 1.12 gm/cc to some of less than 1.0 gm/cc. We have been studying the entire "spectrum" of such lipoproteins in the effort to understand lipid transport. For certain purposes, however, it is convenient (although arbitrary) to segregate the lipoproteins into two major subgroups by means of a cutting point at 1.063 gm/cc. Those lipoproteins of density less than 1.063 gm/cc we have referred to as the "low-density lipoproteins." If such lipoproteins are present in a salt solution of density 1.063 gm/cc, they will undergo flotation when placed in an ultracentrifugal field. In the analytic ultracentrifuge such lipoproteins can be quantitated both as to type and concentration during the process of flotation. A useful mode of characterization of lipoproteins is by use of the flotation rate in Svedberg units† (Sf units) under the arbitrary conditions chosen. Obviously if a medium of density other than 1.063 gm/cc were used for the flotation process, the Sf rates would be altered, but should be perfectly reproducible in the new medium. The study of human serum low-density lipoproteins has revealed

* The experimental work upon which this talk was based is that of a research group, including Hardin B. Jones, Frank Lindgren, Thomas Lyon, Beverly Strisower, Alex Nichols, Dean Graham, N. K. Freeman, and the author.

† Svedberg unit = 10^{-13} cm/sec/dyne/gram.

FIGURE 1—LIPOPROTEIN TRANSPORT AS A MEASURE OF LIPID METABOLIC DEFECT (HUMAN)

"Normal" Pattern

(1) Lipoproteins of Sf4 and/or Sf6 present at low or moderate concentrations. *Minimal* levels of higher Sf components except for transient elevations in Sf30-40,000 following fatty meals.

"Minimal" Defect

(2) Lipoproteins of Sf4 and/or Sf6 at increased concentrations but without any increase in higher Sf components as compared with (1).

"Minor" Defect

(3) Lipoproteins of Sf4 and/or Sf6 *plus* Sf8 in increasing concentration.

Progressively *"More Severe"* Defect

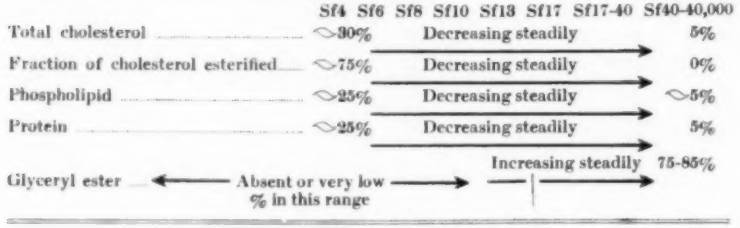
(4) Sf4 + Sf6 + Sf8 + Sf10
(5) Sf4 + Sf6 + Sf8 + Sf10 + Sf13
(6) Sf4 + Sf6 + Sf8 + Sf10 + Sf13 + Sf17
(7) Sf4 + Sf6 + Sf8 + Sf10 + Sf13 + Sf17 + Sf17-20
(8) Sf4 + Sf6 + Sf8 + Sf10 + Sf13 + Sf17 + Sf17-20 + Sf20-40
(9) Sf4 + Sf6 + Sf8 + Sf10 + Sf13 + Sf17 + Sf17-20 + Sf20-40 + Sf40-40,000
(In this group the Sf40-40,000 can be transient existence following meals or may be sustained even post-absorptively.)

(10) *"Most Severe"* Defect
As in (9) except that the Sf4 and Sf6 may be depressed to quite low concentrations. (This may be regarded as a general *shift* toward higher Sf lipoproteins, and is comparable to that which appears in the rabbits in the later phases of cholesterol-Wesson oil feeding.)

species with Sf rates from 2 to 40,000. The Sf 40,000 species is more familiarly known as the chylomicron. Lindgren's work[4, 5] with these lipoproteins has demonstrated several discrete entities; the Sf_2, Sf_4, Sf_6, Sf_8, Sf_{10}, Sf_{13}, and Sf_{17} lipoproteins, differing from one another in chemical structure as well as in physical properties. Above Sf_{17}, and extending to $Sf_{40,000}$, is a host of closely-spaced components, or possibly a continuum of lipoproteins.

Human sera differ from one another in two respects: first, the number of types of lipoproteins present at appreciable concentration; and second, the relative concentrations of the various species present. In spite of a wide variation extant among human patterns, the variations are by no means random. It appears that only certain lipoprotein distribution patterns are allowed. There is a regularity in the development of deviation from a particular pattern, which deviation may be a reflection of a progressive degree of metabolic error in the transport of serum lipids. This concept is illustrated in Figure 1. While there is a regular progression of patterns from those showing only the Sf_4 and/or Sf_6 lipoproteins with inappreciable levels of any species of higher Sf values,

FIGURE 2—CHEMICAL CONSTITUENT



and while the higher classes are never present unless all the lower classes are present at appreciable concentration, there is nevertheless only a partial relation between the serum concentrations of various individual lipoprotein components, even when all of them are present. This fact makes it difficult to predict the level of a particular lipoprotein, from a measurement of total lipoprotein level (or total cholesterol level). For example one individual may characteristically show a ratio of Sf13/Sf17 twice as high as another, even though the total serum lipid levels are comparable. From several lines of evidence our group has developed, it appears, both in the human and in several experimental animals,[5] that the lipoproteins from Sf40,000 to Sf2 are metabolically interrelated. Chemical studies of the lipoproteins by Lindgren, Freeman, and Nichols[6] suggest the nature of this interrelation (See Figure 2). It is seen in Figure 2 that although cholesterol is a constituent of all the lipoproteins, it is a progressively more prominent constituent of the low molecular weight lipoproteins (those of low Sf value). Neutral fat is either absent or a very small fraction of the lipoproteins below Sf17 but becomes progressively more prominent in the higher Sf classes until it is the major chemical constituent in those above Sf 100. The present evidence suggests that fat (and possibly certain other lipids, as cholesterol) of endogenous and exogenous origin may enter this system of lipoproteins in the form of high Sf lipoproteins (Sf30 to Sf40,000). As glyceryl ester is utilized off or transferred out of the blood, the higher Sf lipoproteins give rise to the successively lower members of the series. It is not possible at this time to determine whether a given lipoprotein of the high Sf classes necessarily goes through every one of the lower intermediate classes in the course of metabolism, or what the factors are which determine

exactly where in the higher Sf classes lipid enters the system.

We may inquire now into the significance, metabolically, of elevated levels of the intermediate classes of lipoproteins. If, as the evidence indicates, the lipoproteins are related as an interconversion sequence, elevated levels of the intermediate members may be the result of excessive loading at the input end (the very high Sf classes), or a metabolic block in the rate of transformation from one class to another. In either event the result predicted would be an elevated steady state level of some or all of the intermediate lipoprotein classes. The degree of such a block and its particular position in the transformation sequence would largely determine which lipoprotein classes might be elevated. One major effort in our study of the lipoprotein system is now directed toward an understanding of the nature of the transformation blocking which appears to characterize so large a fraction of the adult human population.

Whatever factor is of major importance in a given case (i.e., excessive loading or transformation block), the human population presents itself with an array of serum patterns differing from one another in the numbers of species of lipoproteins elevated in concentration and in the degree of elevation. The immediate point of interest is the relationship of the serum concentration of individual classes of lipoproteins with the inception and progression of atheromatous vascular disease. It is evident that unless a positive relationship of this sort is demonstrable, considerations of management of atherosclerosis via lipoprotein level control would be meaningless. Ideally the quantitative assessment of the degree of association, if any, of each lipoprotein species with atherogenesis is the goal. Practical considerations of two types limit this, in part, in the human. First it is readily possible to measure a band of lipoproteins, e.g., the total lipoprotein concentration between the limits of Sf10 and Sf20, whereas measurement of the concentration of a single species, e.g., Sf13 or Sf17, may be difficult. Secondly, assessment of the rate of atheroma formation in the living human is beset with difficulties. No direct measurement of this rate is available. A somewhat crude first approximation to this can be made by choosing a clinical entity largely superimposed upon an atherosclerotic background, such as clinically manifest coronary artery disease and comparing this with a group of presumed normals of the same age and sex. The assumption, which is a reasonably safe one, is that on the average atheroma formation is

proceeding in the coronary vascular bed at a greater rate in the frankly diseased group than in the normals. At best, we know from autopsy and other data that the "normals" are also atherosclerotic, although they are developing the disease with a rate of the order of ½ to 2/3 that of the "diseased" group. Further, the focal character of atherosclerosis will necessarily place certain individuals with minimal total atherosclerosis in the "diseased" category, when actually their rate of atherogenesis is less than that for many of the "normals." Other factors also operate to obscure our assessment. The categorization of an individual as a "coronary" is a reflection not only of present rate of atherogenesis but also of *accumulated* atherosclerosis with its associated arterial narrowing. In addition, there is the possibility that at a given time an individual may be developing atherosclerosis at a different rate from that which prevailed at other periods.

The above-described obstacles in reaching the goal, measurement of association of lipoproteins with atherogenesis, are indeed formidable, but not insuperable. Their existence, however, makes it important to realize that whatever quantitative correlation is found between certain lipoproteins and atherogenesis is a *minimum* one. The true correlation must undoubtedly be much better than that which we measure, since all the obscuring factors have the effect of reducing the measurable relation.

Quantitative Measurement of the Relationship of Lipoproteins with Atherosclerosis

In the experimental rabbit we have been able to produce a "spectrum" of lipoproteins generally similar in properties to that in the human. It has also been possible to show in the rabbit that the rate of accumulation of atheroma is almost perfectly associated with the serum level of certain special classes of lipoproteins, but that it is not associated (or even inversely associated) with the serum levels of certain other classes.

In making the assessment of the lipoprotein-atherosclerosis relationship in the human it is convenient to compare with the observed relationship of serum cholesterol. Small segments of the lipoprotein "spectrum" can be tested for association with atherosclerosis at the same time the serum cholesterol is tested and the relative relationships determined. In such testing procedures it has been possible to show that two particular

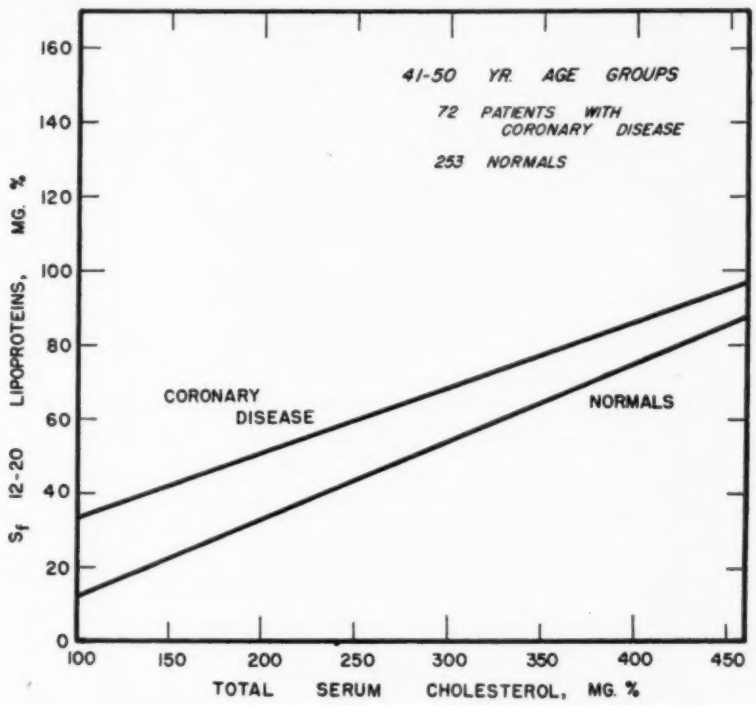


Figure 3a

Figure 3(a)—The lines shown represent the average values of the Sf12-20 lipoprotein levels for any given cholesterol level. It is seen that patients with coronary disease show higher Sf12-20 lipoprotein levels than do normals having the same serum cholesterol, throughout the range of serum cholesterols. Thus the Sf12-20 lipoproteins have the ability to segregate coronary patients from normals *independent* of the serum cholesterol. (Reprinted by permission from the American Journal of Medicine, v. II, 1951.)

segments are of especial interest, namely, the band of lipoproteins from Sf_{12} to Sf_{20} and the band from Sf_{20} to Sf_{100}.[7, 8] A useful means of expressing the findings is at hand in the form of the "regression lines" between serum cholesterol and the particular lipoprotein class being considered. In essence such lines are simply a plot of the average lipoprotein level at each serum cholesterol, or conversely the average serum cholesterol level at each lipoprotein level. Figures 3 (a), (b), and (c) present the critical data for 41-50 year old male "normals" and coronary

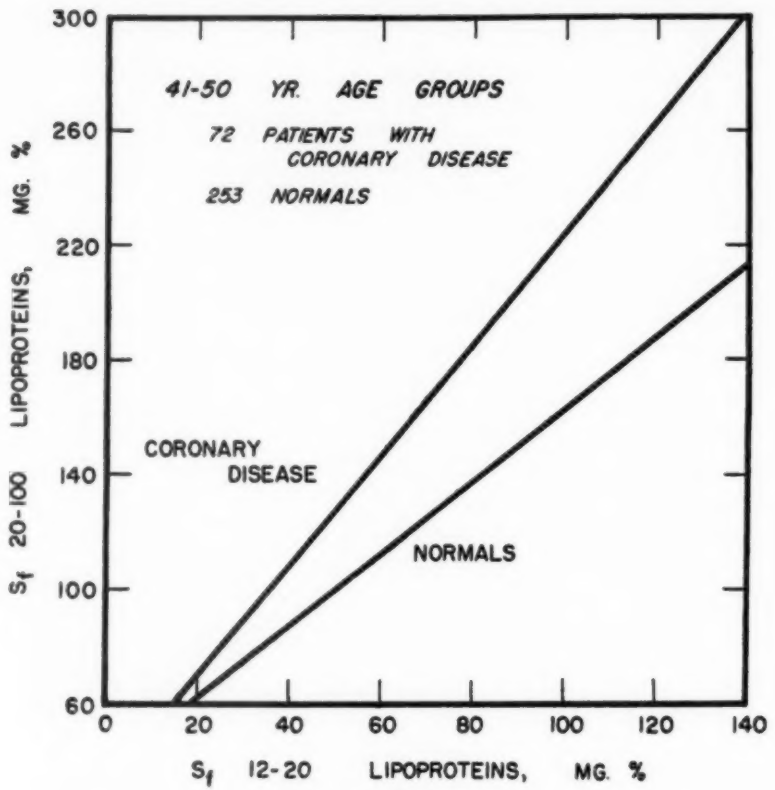


Figure 3b

Figure 3(b)—The lines shown represent the average values of the Sf20-100 lipoprotein levels for any given Sf12-20 lipoprotein level. It is seen that patients with coronary disease show higher levels of Sf20-100 lipoproteins than do normals having the same Sf12-20 level. Thus it is evident that the Sf20-100 lipoproteins segregate patients with coronary disease from normals independent of the segregation achieved by the Sf12-20 lipoproteins. Both classes of lipoproteins, the Sf12-20 and Sf20-100, are of importance for atherosclerosis. Both groups are associated with atherosclerosis, independent of the serum cholesterol level. (Reprinted by permission from the American Journal of Medicine, v. II, 1951.)

patients for serum cholesterol, the Sf_{12-20} lipoproteins, the Sf_{20-100} lipoproteins, and the combined Sf_{12-100} lipoproteins. Consideration of these figures leads to several important conclusions:

1. The band of lipoproteins from Sf_{12} to Sf_{20} (the "Sf_{12-20} class") is higher in the coronary group than in the normal group even

FIGURE 3c—COMPARISON OF THE Sf12-100 LIPOPROTEIN-ATHEROSCLEROSIS RELATIONSHIP WITH THAT OF THE REMAINING BULK OF SERUM CHOLESTEROL

(72 Patients with Coronary Disease)
Mean Serum Cholesterol = 304 mg. % (Standard Error = 4 mg. %)
283 Normals Mean Serum Cholesterol = 260 mg. % (Standard Error = 6 mg. %)
Difference in Serum Cholesterol = 44 mg. % (Standard Error = 7 mg. %)

Lipoprotein Class	*Difference between coronary patients and normals (In mg.% lipoprotein)*	*% Cholesterol** in Lipoprotein Class*	*Difference between coronary patients and normals in mg.% cholesterol*
Sf10-12*	8.2 mg.%	30%	2.5
Sf12-20	23.9 mg.%	25%	6.0
Sf20-100	72 mg.%	20%	14.4
Sf100*	20 mg.% (Minimum estimate)	~6%	1.2
			Sum = 24.1 mg.%

From the independent measurement of the intercorrelation of the Sf12-20 lipoproteins with the Sf0-8 lipoproteins, the coronary group should be 32 mg.% higher in Sf0-8, on the basis of this intercorrelation alone. Sf0-8 lipoproteins contain 35% cholesterol. Thus (32) (0.35) = 11.2 mg.% cholesterol is *expected* difference between coronary and normal population. This may be added to the 24.1 mg.% already accounted for since it represents no *independent* contribution of the Sf0-8 lipoproteins.

Thus 24.1 + 11.2 = 35.3 mg.% cholesterol difference is accounted for in Sf10-100+ class of lipoproteins.

Remainder 44 — 35.3 = 8.7 mg.% cholesterol.

This small remainder, which cannot be proven significant from these data, is all that remains for possible independent contribution from the remaining bulk (~85%) of the serum cholesterol to atherosclerosis. It is evident therefore that this bulk of serum cholesterol shows very little, if any, independent association with atherosclerosis.

* Sf10-12 lipoprotein levels correlate very highly (r = 0.8) with Sf12-20 lipoprotein levels. Sf100+ lipoproteins correlate highly with Sf20-100 lipoproteins.
** See reference 6.

when both groups are compared at identical serum cholesterol levels, over the entire serum cholesterol range.

2. The band of lipoproteins from Sf20-100 (the "Sf20-100 class") is similarly higher in the coronary group than in the normal group even though the serum cholesterol levels are identical.

3. The data in Figure 3c indicate that essentially the entire difference in serum cholesterol between "coronaries" and "normals" is accounted for by the Sf12-100 lipoproteins, or by those elevated solely through intercorrelation with the Sf12-100 lipoproteins. This finding implies that the remaining lipoproteins are of a lesser degree of atherogenicity than are those of the Sf12-100 group. It implies further that the important lipoproteins of the Sf12-100 class are masked by the much

larger bulk of lipoproteins (approximately 85 per cent of the total lipoproteins) that are being assessed primarily when a serum cholesterol measurement is made. On the other hand the general trend toward rising Sf12-100 lipoprotein level with rising serum cholesterol levels means that as a crude first approximation the serum cholesterol level will show some correlation with atherosclerosis, although this correlation is less than that for the Sf12-100 lipoproteins with atherosclerosis. Further since the Sf12-100 level can be high when the total cholesterol is low, or low when the total cholesterol is high, individual cases may be seriously misclassified as to atherogenic potentialities by a simple serum cholesterol measurement.

The question may now again be raised as to the actual strength of the relationship between the Sf12-100 lipoproteins and atheroma development. From the earlier consideration of obscuring factors we can be assured that the true strength of the relationship is much greater than that which we have been able to demonstrate. Reasonable estimates of how much obscuring factors might reduce the observed relationship together with estimates of errors in measurements[5] have led us to the conclusion that the Sf12-100 lipoproteins account for the great bulk of the general metabolic factors which lead to atherosclerosis.

There is, then, a class of lipoproteins in human serum highly associated with atheroma development. It cannot be proven at this time that this association is an etiologic one. However, our concept of atherosclerogenesis is that the lipids of lesions originate from the blood, and it is hence highly likely that the Sf12-100 lipoproteins represent the actual blood source of those lipids. Unless the developing evidence should contradict this view, it may be considered feasible to attempt the management of atherosclerosis through measures directed toward the reduction of the serum level of the Sf12-100 lipoproteins. It is worth pointing out here that the objective is not necessarily reduction of total serum cholesterol levels.

Thus if a shift from the atherogenic Sf12-100 lipoprotein classes to other less atherogenic or non-atherogenic lipoproteins could be produced without any drop in total serum cholesterol level the desired objective might be attained. Conversely if a drop in serum cholesterol is achieved with a concomitant shift into the Sf12-100 class, the effect would very likely be an increase in atheroma formation rather than a decrease.

Dietary Approaches to Atherosclerosis

(a) *Caloric intake and obesity:* It is a matter of fairly general agreement that obesity is almost wholly the result of the ingestion of an excess of calories in the diet. Clinical and insurance experience[9] have shown that a positive relationship exists between obesity and atherosclerotic vascular disease. No satisfactory explanation of this relationship has been adduced from the semi-popular view of an excessive "work burden" for the heart. Our own evidence suggests a very different basis for this relationship of vascular disease to obesity. Since the Sf12-100 lipoproteins are associated with atherosclerosis, we have endeavored to assess the extent to which obesity contributes to elevation in the serum Sf12-100 lipoprotein level. Ideally a direct estimate of the body fat content of the studied subjects should be made. Since such measurements were not available during the study, a crude measure of obesity was obtained from height and weight measurements and a table of ideal height-weight relationships.[10] In a group of 253 male subjects a definite positive correlation was found between estimated obesity and Sf12-100 lipoprotein level (crude correlation coefficient = 0.3). If account is taken of two factors, the crudity of height-weight measures as an estimate of obesity and the biologic and technical variation in Sf12-100 lipoprotein measurements, it becomes certain that the true relationship of Sf12-100 lipoproteins with obesity must be considerably higher than the measured one. A reasonable estimate of such factors indicates that the order of 20 per cent of the factors contributing to elevation of the Sf12-100 lipoprotein levels are directly related to obesity. This means that obesity may account for approximately 20 per cent of atherosclerogenesis via the Sf12-100 lipoproteins.

The practical, clinical implications of this relationship deserve to be stressed. The "normals" who escape manifest coronary artery disease have atherosclerosis, but of lesser quantitative degree than do patients with frank coronary disease (perhaps of the order of 30 per cent less). Therefore reductions in rate of development of coronary atherosclerosis of 10-20 per cent might be anticipated to provide a very significant decrease in the occurrence of clinical sequelae of coronary sclerosis. It can be predicted that reduction of caloric intake and, hence, correction of obesity may certainly be expected to do at least this much on the basis of the Sf12-100 lipoprotein relationship with overweight. Our ex-

perience with patients has amply indicated reduction in Sf12-100 levels as caloric intake is dropped and obesity is lessened. There is considerable individual variation in the extent of Sf12-100 lipoprotein reduction which results from caloric restriction and weight loss. This individual variation is, however, to be expected since the correlation of Sf12-100 level with overweight is quite definite but not high enough to assure uniformity of response. In certain individuals the drop in Sf12-100 level associated with weight loss is quite marked and may well ultimately prove to be a major factor in prevention of premature coronary disease. It has been suggested that the mobilization of endogenous fat during a period of weight loss might result in elevation of the serum levels of certain lipoproteins and that this might be deleterious. At present our experience indicates that the Sf12-100 lipoprotein levels fall during the actual period of weight loss. However, it is conceivable that further study of this problem may show that in certain individuals a rise in level may occur during weight loss.

(b) *Dietary Fat Intake:* Since at least part of the fat in the various lipoprotein classes is of exogenous origin,[11] it is of importance to know to what extent dietary loading with fat results in elevation of the Sf12-100 levels. The investigation of lowering fat intake clinically is hampered by the fact that the patients studied generally tend to lose weight, at least in the initial periods of fat restriction. This weight is not usually regained in the patients who continue to adhere to the low fat diet. Thus even though such patients show, in a high proportion of cases, a significant lowering in Sf12-100 levels, it is difficult to segregate out that part of the effect due to lowering of caloric intake and weight from that due to lowered dietary fat loading.

However, in other patients studied the serum Sf12-100 lipoprotein level drops even when there is no appreciable weight alteration on a diet restricted in total fat intake. These studies indicate an effect of the dietary fat separate from the calorie-weight effect. The human population appears quite inhomogeneous in this response to fat restriction. At present it is not possible to predict which patients will respond to dietary fat restriction from the lipoprotein pattern or from any other consideration. Excluding cases where the diet has not been adhered to, there are still unquestionably cases where fat restriction does not reduce Sf12-100 levels. The initial lipoprotein pattern in such individuals does not appear significantly different from that in cases where restriction in

fat does produce drops in Sf12-100 levels. At present the individual's response to a lowering of fat intake is determined by actual trial, with serial lipoprotein studies.

Thus dietary measures, including caloric restriction and fat restriction are capable of reducing elevated Sf12-100 lipoprotein levels in a part of the human population. Neither measure is universally effective in reducing lipoprotein levels. However, the response to one or another of the measures is of sufficient degree and frequency to warrant the trial of a low fat diet plus obesity correction as an approach to Sf12-100 lipoprotein reduction in the management of atherosclerosis.

"Lipotrophic" Agents

The desirability of a pharmacologic approach to the lowering of the Sf12-100 lipoprotein level is self-evident, if we accept the hypothesis that these serum lipoproteins represent the source of atheroma lipids. There might well be objection to the use of the term "lipotrophic agent" to describe a substance capable of reducing the Sf12-100 level. Possibly the only justification for the use of this term with respect to the present problem is the fact of its widespread use in this connotation.

The one pharmacologic agent showing a marked effect upon the Sf12-100 levels and upon serum lipoprotein distribution in general is heparin. A detailed publication of the findings of Graham et al of our laboratory has appeared.[12] The effect of heparin upon the serum lipoproteins in the human is of especial interest since it appears to be such as to shift lipoprotein patterns in the direction of normality. Subsequent to the injection of a single dose of 25-100 milligrams of heparin intravenously, there is a progressive reduction in levels of the lipoproteins of very high Sf classes (above Sf20) with transitory increases in the intermediate classes (Sf10-20 class). Subsequently the Sf10-20 lipoprotein level may decrease with a concomitant rise in the level of lipoproteins below Sf10. The reduction in level of lipoproteins above Sf20 (Sf20-100 and higher classes) is striking within 5 to 20 minutes following intravenous heparin injection. The progressive transformations continue over a period of several hours. Within 24 hours after a single heparin dose in the range of 25-100 milligrams most humans show a reversion to the pre-heparin lipoprotein pattern. Most striking of all the changes is the ability of heparin to produce essentially a "wipe-out" of the serum lipoproteins above Sf20. Since a major constituent of the

lipoproteins above 20 Sf units is glyceryl ester (neutral fat), this represents a removal from the entire blood volume of quantities of the order of several grams of fat. The fate of the fat thus cleared from the blood is now under investigation. In general it appears that the dose of heparin required to wipe out the Sf20-100 lipoproteins is greater the higher the level of such lipoproteins originally.

Since the shift in lipoproteins under the influence of heparin is in the direction that normal interconversion pathways appear to follow, it seems possible that heparin in a combined form, or some related system, is normally involved in lipoprotein interconversion in the human. Abnormal serum lipoprotein distributions might then be the result of a quantitative inadequacy of heparin in the appropriate form for handling the lipid load. This question is now under active investigation.

The serum lipoprotein shift produced by heparin appears favorable with respect to the atherosclerosis problem since the level of the atherosclerosis-associated Sf12-100 lipoproteins is markedly reduced. Graham et al[12] have shown that heparin suppresses the rise of Sf10-50 lipoprotein levels and suppresses atherosclerosis in the cholesterol-fed rabbit. The possibilities of similar application of heparin in human atherosclerosis would be facilitated by the availability of an acceptable long-acting heparin, so that the Sf12-100 lipoproteins might be chronically suppressed. The effects of long-term use of heparin for the purpose of lipoprotein alteration will become clarified as a result of further studies. In any event this agent has produced striking alterations in lipoprotein distributions which assure the possibility, at least, of lipoprotein control through pharmacologic means. If it also sheds light upon the naturally-occurring factors which account for normality or deviation therefrom in lipoprotein transport, atherosclerosis research will have been materially advanced.

Summary

1. The ultracentrifugal study of human serum allows the characterization of lipid transport in terms of a "spectrum" of lipoproteins.

2. The type of lipoprotein transport characteristic of an individual is apparently a reflection of the degree of deviation from normal lipid metabolism.

3. Certain of the lipoprotein classes, the Sf12-20 and Sf20-100 classes, show a high quantitative association with atherosclerogenesis in

the human. This association is manifest independent of total serum cholesterol level.

4. Obesity is associated with elevation of the Sf12-100 lipoproteins. This association may be adequate to account for the excessive atherosclerosis in the obese.

5. Reduction in caloric intake and weight reduces Sf12-100 levels to a variable degree in the human population. Reduction of dietary fat has a similar effect in part of this population.

6. Heparin administration to humans produces a shift in lipoprotein patterns toward normal.

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THE IMPORTANCE OF CARDIAC ARRHYTHMIAS*

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It is a privilege to participate in the 24th Graduate Fortnight, which represents the joint efforts of The New York Academy of Medicine and the New York Heart Association, a most important affiliate of the American Heart Association.

The subject of the irregularities of the heart is an old one but it needs review. It constitutes an important area of clinical medicine that the physician needs to know thoroughly. Cardiac arrhythmias are divided into (a) disturbances in impulse initiation, and (b) disturbances of impulse conduction.[1]

The impulse for the heart beat may arise in the primary pacemaker, the sinus node, or in some ectopic pacemaker outside the sinus node. When it arises in the sinus node, it may be a regular sinus rhythm, with a regular periodicity somewhere between 60 and 100 beats per minute. It may be faster than this, sinus tachycardia. It may be slower, sinus bradycardia. It may be irregular in its rhythm, sinus arrhythmia. The irregularity in sinus arrhythmia is often obviously associated with respiration and is therefore called phasic; sometimes it is not and is then known as nonphasic. The impulse in sinus arrhythmia may come from one focus or it may wander from one part of the node to another. The latter is known as a wandering sinus pacemaker.

When the pacemaker is outside the sinus node, such an ectopic rhythm may be a passive one, occurring when there is depression of the primary pacemaker or blockage of its impulse. This may appear as a persistent nodal rhythm (of the A-V node) or it may be an occasional nodal escape; it may be in the form of an idioventricular rhythm associated with complete A-V heart block. Rarely, it may be a ventricular escape. It may be a wandering of the pacemaker between the sinus pace-

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maker and the secondary one, the A-V node, a perfectly normal phenomenon.

Ectopic rhythms may be active, the most common being premature systoles. These ectopic rhythms may be of A-V nodal, auricular or ventricular origin, rarely of sinus node origin. They may be in the form of paroxysmal tachycardia, supraventricular or ventricular in origin. They may be in the form of chaotic heart action. More commonly they are auricular flutter or auricular fibrillation. Rarely, they may be ventricular flutter or fibrillation, most often a terminal event, but on rare occasions, paroxysmal.

In the case of disturbances of impulse conduction, one should distinguish between the expression of the normal physiology of the conducting system, that is the phenomenon of the normal refractory period, and actual depression of the conduction process with abnormal prolongation of the refractory phase. Since the heart must beat intermittently if blood is to be pumped, it is obvious that its inability to respond again immediately after stimulation is valuable. This is due to the presence normally of a long refractory period. Should a second impulse reach a part of the heart during such a refractory state then it will not be transmitted at all or it will be delayed in its transmission. This phenomenon is called isolated interference (when one beat is affected) or dissociation (when several beats are affected in succession).

Interference and dissociation are to be distinguished from heart block. In heart block the transmission of the impulse is delayed or prevented because of disease of the heart which leads to an abnormal prolongation of the refractory period. Such block may be between the sinus node and the auricle (S-A block); and this is usually vagal in origin and most often due to digitalis. It may be within the auricles (intra-auricular block), which is recognized only in the electrocardiogram by irregularities and prolongation of the P wave. It may be between the auricles and ventricles (A-V block) and appears in many varieties. It may be within the ventricles, intraventricular block or bundle branch system block, involving either the right bundle branch system, the left bundle branch system, or both, besides the isolated and focal varieties. Alternans of the heart may be considered, as a first approximation, to be a focal form of heart block of the 2 to 1 variety. A different form of conduction disturbance is the phenomenon known as Wolff-Parkinson-White syndrome, due to an anomalous rapid A-V by-pass, a congenital anomaly.

The statistical frequency of these arrhythmias may be gleaned from the experience of the Heart Station of the Michael Reese Hospital, the clientele of which is a mixture of private and service cases, in- and out-patients, of various racial origins. It is therefore a fair cross-section of urban practice. In about 25,000 cases with 50,000 records,[1] there were about 14,000 instances of regular sinus rhythm. About 3000 cases were sinus tachycardias, about 1000 were sinus bradycardia, and about 6000 were sinus arrhythmias, the vast majority being phasic.

There were about 200 instances of persistent nodal rhythm, about 100 instances of nodal escape and about 500 cases of wandering pacemaker. Premature systoles, which I believe we have all had at one time or another, occurred over 2000 times, the ventricular variety being by far the most common. Paroxysmal tachycardias occurred over 150 times; however, their frequency is apt to be underestimated because the attack is usually over before a record is obtained.

Fibrillation of the auricles occurred about 1500 times, next in frequency to sinus arrhythmia and premature systoles as a cause of irregular beating of the heart. Auricular flutter occurred about 100 times. Ventricular fibrillation was extremely rare.

A-V heart block constituted something like 700 cases, the majority of which were not recognizable at the bedside but only on the electrocardiogram. Other forms of block were not common except for intra-auricular and intraventricular block both diagnosed by the electrocardiogram.

I would like to stress the fact that the study of the cardiac arrhythmias is one of the best ways to learn about the physiological properties of the human heart. I would recommend this exercise to all of you. It has been a matter of continuous wonder to me how much we can learn about the heart by unraveling the various arrhythmias.

From such an analysis of the arrhythmias and some animal experiments, we can appreciate the role of the specialized heart tissue in impulse formation and transmission.

The specialized heart tissue is of two varieties. There is the nodal tissue which excels in giving rise to the impulses which govern the heart beat. It is not nervous tissue, it is not embryonic tissue, but neomorphic muscular tissue. It consists of the sinus node, the A-V node and islets of nodal tissue located in the auricles and in the ventricles, in the latter in close association with the second variety of specialized heart tissue,

the Purkinje system. The Purkinje system is primarily a rapid transit system for the ventricular myocardium. This tissue too is neomorphic. There are sufficient observations in man to substantiate the presence and importance of these two specialized muscular systems.

The physiology of clinical arrhythmias is still a matter of great current interest and lively concern. This can be illustrated by several examples.

1. I have recently reviewed a record which the late Dr. W. W. Hamburger had obtained in the 1920's; at that time it was considered a bundle branch block. It was obviously an instance of the Wolff-Parkinson-White syndrome. This case, recently reported by my associates Malinow and Langendorf[2] was still found to have the same condition some twenty years later. He had had a history of paroxysmal tachycardia for years, but had no organic heart disease and was clinically well. He simply had this congenital anomaly of the conducting system. This is to my knowledge, the longest lasting case on record.

2. As a result of the recent studies of Scherf and Prinzmetal the circus movement theory of Lewis concerning auricular flutter and fibrillation has been called into question. In the early thirties, Brams and I,[3] at the Michael Reese Hospital demonstrated that post-faradic auricular flutter and fibrillation in the dog with open chest, persisted when the auricles were clamped or cut in the region over which the "mother ring" was supposed to be located. We used this as evidence against the simplified circus movement theory and it is therefore pleasing to me to have this subject under scrutiny once again. Recently also multiple precordial and esophageal leads have revealed isolated auricular waves of large size, which were going at rates of 300 or more, separated by quiescent periods in some cases of auricular flutter and fibrillation. This finding also is difficult to reconcile with the simple circus movement theory. The mechanism of this type of arrhythmia is thus once again a matter of active study and the final answer is still not available.

3. Recently a valuable addition to our therapeutic aids has been made available in the form of procaine amide. This we,[4] like others, have studied and found to be an excellent substitute for quinidine. In brief, it behaves like quinidine including its undesirable side-action. It may be used in place of quinidine and should be especially valuable when there is an idiosyncrasy to quinidine.

I would like to point out that when we deal with the cardiac

arrhythmias, we are dealing with disturbances in both rate and rhythm. In the case of paroxysmal ventricular tachycardia, for example, we often find intermittent periods of sinus rhythm between the periods of rapid ventricular beating. A glance at any record will also show how prolonged is the QRS duration of these ectopic beats. Thus, not only do the ventricles beat extremely rapidly but the time occupied in their stimulation is prolonged. This is a very wasteful method of beating mechanically, and so cuts down decidedly on the mechanical efficiency of the beat.

Sometimes the rates of the human heart are extremely rapid. I have on occasion seen a ventricular rate in man persistently over 300. There are some birds like the humming bird that have rates over 1000 per minute. At other times the human heart is extremely slow. I have seen cases with persistent rates as low as 18 per minute or even slower.

In auricular fibrillation the rate is grossly irregular. Sometimes the average rate is fast, approaching 300, at other times it is extremely slow. Complete A-V block may occur in auricular fibrillation, sometimes as a result of too much digitalis, and it is possible that the idioventricular pacemaker may fail to discharge leading to heart standstill. Or the digitalis medication may cause frequent premature systoles to appear and this carries the hazard of leading to runs of such premature beats and even to ventricular fibrillation which is usually terminal. Ventricular fibrillation is only rarely reversible, although I, like others, have seen such cases.

What is the importance of arrhythmias? The first thing, I should like to stress is that arrhythmias are often functional, although they are, of course, sometimes due to organic heart disease. The thing the clinician should first assume when he finds a disturbed heart action, whether it be tachycardia, bradycardia or irregularity, is that he is dealing with a functional disturbance, possibly a manifestation of psychosomatic disturbances. He should, of course, thoroughly examine the patient to rule out organic heart disease but he should constantly remember that disturbances in heart action are often functional and sometimes psychosomatic. Winton, Megibow and I[5] have recently described an interesting case of paroxysmal auricular tachycardia definitely brought on by emotionally traumatic life situations. Almost any kind of arrhythmia may be caused by psychosomatic disturbances.

These psychosomatic disturbances in rhythm are in all likelihood the

result of reflexogenic phenomena with the effector organ the heart, and the pathways involving the nerves regulating the heart. In addition hormones play a role, especially those of the adrenal medulla, in modifying the heart's behavior. Such patients have anxiety. The thing that I would like to stress, is that in such cases the physician's handling of the case is of vast importance. If the doctor makes too much ado about the heart action, if he looks too long at the electrocardiogram, if he says, "Oh, you have an irregular pulse, it is just *nervousness*"—a word taboo to most patients—or casually remarks "forget about it," he may produce an anxiety neurosis, a "cardiac fixation." With the world full of people maladjusted in business or in family relations, a cardiac fixation is an excellent escape.

The palpitation associated with an irregular heart action is often disturbing even to well-adjusted people, and may become progressively more and more psychologically painful until it imitates the discomfort of an anginal attack. I have read an excerpt published by the late Soma Weiss of Boston from the diary of an intelligent medical student who was troubled with simple ventricular premature systoles. His description of the exquisite discomfort, the fright, the emotional unhappiness it created, even though he appreciated its benign quality, should warn us of the effect of irregular heart action upon less sophisticated persons who tend to be easily frightened by anything wrong with the heart. This discomfort I am sure all of you have experienced in one form or another at some time. Consequently I am sure you will be kind, solicitous and careful with patients who have cardiac arrhythmias.

By and large, the treatment of arrhythmias is symptomatic. If they cause no trouble, they ordinarily require no therapy. With one or two exceptions there is no specific therapy for arrhythmias. Reassurance is important. Attacking the underlying disease, when it is organic, will do a great deal to alleviate the large group of arrhythmias associated with organic heart disease.

It seems to me that the old-fashioned art of medicine is being lost in this era of instruments. A precise instrument does not necessarily make things more quantitative since the judgment still depends on human beings. We must therefore remember the entire patient when we are dealing with cardiac arrhythmias and plan our therapy accordingly. That is the true art of medicine.

There is specific treatment for some of the arrhythmias under cer-

tain circumstances. I would like to point out just one or two examples. Quinidine and papaverine are "soothing agents" for active ectopic rhythms. Papaverine is useful in this regard though not as potent as quinidine. Pronestyl (procaine amide) has been recently added for this same purpose.

In chronic coronary disease, in chronic coronary insufficiency, the exhibition of quinidine is extremely valuable when premature ventricular systoles are found. It helps in these circumstances to prevent unexpected deaths, and it may help to avoid angina and heart failure.

Then there is the specific therapy of what we call the Stokes-Adams syndrome, complete A-V heart block. It should be called the Morgagni-Stokes-Adams syndrome. There are several useful drugs for it. However, all I wish to point out at this time is that in the presence of complete heart block, the convulsions and unconsciousness are many times due to inadequate circulation arising not from slow heart action, but by virtue of intermittent paroxysmal ventricular tachycardia. Under such circumstances the exhibition of drugs like adrenalin or some of the other sympathomimetic drugs may, as we found, clinically aggravate the condition of the patient instead of benefiting him. Therefore the first thing to do is to find out whether the mechanism causing the symptoms is due to slow ventricular action or to excessively rapid action.

The bedside diagnosis of arrhythmias can be developed by training and perseverence. We can diagnose many of the arrhythmias by looking at the jugular pulse, by palpating the heart and the radial artery, although the electrocardiogram is in almost all occasions the living autopsy with which to verify whether or not our judgments are correct. As a matter of fact that is the way in which the diagnosis should be attempted, the electrocardiogram should not be used as the first line of evidence but to substantiate clinical judgment.

The prognosis of the arrhythmias is dependent upon the underlying disease. Some twenty years ago, when I first became interested in this subject it was thought that persons with bundle branch system block had a definite prognosis—50 per cent of them would die in two years and 25 per cent in two months. Actually, when we analyzed this matter further, it became obvious that the statistics were due to the underlying diseases causing the block.

In the case of ventricular premature systoles of frequent origin, and in the presence of ventricular paroxysmal tachycardia, associated with

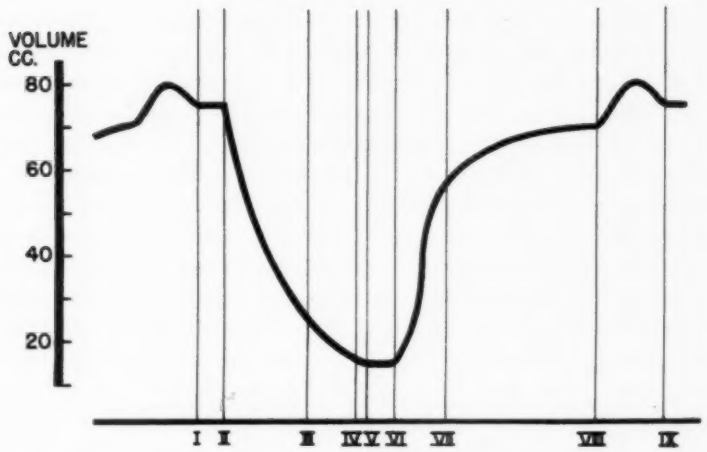

Fig. 1—Diagram of the volume curve of one ventricular cavity of the human heart at an assumed rate of 80 beats per minute, a stroke volume of 60 cc. and a systolic residue of 15 cc. based on the studies of Wiggers and Katz.[6] Discussed in text.

organic heart disease, I am always fearful that unexpected death by ventricular fibrillation may occur. Nevertheless it is unwise to prognosticate solely from the arrhythmia. This is one of the ways in which electrocardiography has been improperly used.

Arrhythmias themselves lead to symptoms. They can lead to heart failure, both the forward failure variety with low output, and the backward failure type with congestion. I am sure all of you have seen cases of paroxysmal tachycardia with cyanosis, congested veins, tender livers and shortness of breath—all of which quickly disappear once the mechanism is broken. Angina pectoris is actually often induced in the presence of coronary disease or coronary insufficiency by rapid heart action or cardiac irregularity.

To understand how this comes about it is necessary to appreciate the volume curve of the ventricles. This is shown in Figure 1 and is based on the work of Wiggers and myself in 1922.[6] This expresses the way the dog's heart contracts, and it has been verified, in caricature, by the electrokymograph of the ventricular surface of the human

heart.[7a] The curve starts in diastole. When the impulse in the sinus node spreads to the auricles it causes them to contract and then relax (between VIII and IX and the homologous part of the curve ahead of I). The auricles contribute very little to filling; about 5 cc. net out of the total of 60 cc. at ordinary heart rates. Actually while they add 10 cc. during their systole they "take back" 5 cc. during their active relaxation. They are antechambers, not important pumps. The impulse reaches the ventricles at I, and they begin to contract, at first isometrically (between I and II). This is a presphygmic period or, as Wiggers has named it, the isometric contraction period, where the ventricular cavity does not change its volume and only its pressure rises. Then ejection begins. In this short period of time, from II to IV, the blood is ejected from the ventricle (that is, all but the systolic residue of about 15 cc.). Most of the blood is ejected during the rapid ejection period (II to III) and the small remainder in the reduced ejection period (III to IV). Diastole begins at IV with a short protodiastole phase (IV to V) and an isometric relaxation period (V to VI) during which the ventricle is relaxing isometrically, that is, without changing the volume of its cavity.

The point I wish to stress above all, which is not as widely appreciated as it should be, is that most of the filling of the heart occurs in the rapid inflow phase (VI to VII), and that filling here is just as brusque, and the period of filling is just as short, as that of the rapid ejection phase. In other words, the heart fills with a rush over a short period and not deliberately and uniformly over the whole of diastole. After the rapid inflow is the period of passive filling, diastasis (VII to VIII), due to the vis-a-tergo of the blood coming back to the heart. From this analysis it is obvious that the rapid emptying and rapid filling of the heart occupy only short periods of the cycle.

With this background of the manner of the ventricular contraction and relaxation let us consider the effect of tachycardia. If we ignore compensatory mechanisms for the moment and assume that the only thing that will affect the output of the heart is the Starling effect, that is, that the stroke volume is a function of the end-diastolic volume of the ventricle, then it is obvious that as the rate speeds up from 80 beats per minute, the diastolic volume will decline and with it the stroke volume. At first these changes will be small because it will be the period of diastasis which is cut short. Hence the product of heart

rate multiplied by stroke volume—which determines the minute volume—will increase. Thus up to rates of roughly about 150 or 160 or thereabouts the cardiac output per minute will tend to go up unless compensatory mechanisms prevent it. At first therefore tachycardia is beneficial in that the heart is able to pump out more blood per minute.

But when the heart rate gets faster than about 160, there is an encroachment upon the rapid inflow phase. Hence diastolic volume and stroke volume decrease more rapidly and soon the decrease in stroke volume is greater than the increase in heart rate and consequently their product, the minute volume output, declines. So tachycardia beyond a certain point cuts down the minute volume output unless compensatory mechanisms can make it up. Tachycardia of marked degree leads to heart failure, and that is sometimes seen in paroxysmal tachycardia.

It is conceivable to imagine a rate so rapid that the heart starts its systole before filling begins. Under these conditions all it can pump out therefore would be the systolic residue (of about 15 to 20 cc.). Hence pumping would soon stop. That this can occur for a beat or so is known. We have recently recorded the pressure pulse of the human aorta by passing a catheter into it[7b] and have noted ventricular premature systoles so early that even in the aorta there was no register of the beat of the heart.

Compensatory mechanisms will tend to make up for the deficiency of rapid heart action but tachycardia beyond a certain point, despite such compensation, will become detrimental and can lead to circulatory insufficiency.

Tachycardia when excessive may also become detrimental because with increasing heart rate the coronary flow becomes less adequate and eventually coronary insufficiency develops. This is revealed in the electrocardiogram as the post-tachycardia syndrome, with its coronary-like S-T-T complex.

Furthermore, as the heart speeds up, because the duration of systole varies with the square root of the cycle length, the heart spends more of its time in systole and less in diastole. That is, the heart as it speeds up works longer and rests less. Since the heart cannot go into oxygen debt to any appreciable extent,[8] it is hard put to recover during its abbreviated diastole from the work done in its systole. This is another detrimental effect of tachycardia.

If one calculates the mechanical efficiency, i.e., the work done over the energy utilized to do the work (using similar units), it can be shown that the efficiency of the heart as a machine goes down decidedly when it speeds up. This too is a detrimental effect of tachycardia.

Thus, while tachycardia may be essential in fever, heart failure and the like, for the heart to do its job, it is an inefficient and relatively costly way of doing it, and may lead by itself to troublesome circumstances, particularly in the presence of organic heart disease. It may hasten or aggravate failure of the heart and it may be the trigger causing angina pectoris.

Bradycardia also leads to circulatory disturbances. It has been demonstrated that the heart cannot increase its stroke volume, ordinarily by more than four-fold. That is, its stroke output cannot exceed approximately 250 cc. If the heart rate goes down markedly, the output per minute, the product of rate times stroke volume, may be adequate for rest, but when the patient gets up and around, it may become inadequate and forward failure may develop. Is it surprising that under circumstances of emotional or physical stress, such a patient develops the signs of congestive heart failure or faints?

Two other facts about bradycardia need to be mentioned. One is that there is a large pulse pressure in bradycardia, and that in the presence of a roughened aorta, a diastolic murmur sometimes may occur. This murmur arises because eddies are set up, of a frequency audible to the ear, as blood moves backward to the heart over the roughened aorta immediately following systole. Velocity pulses in animals show the presence of this temporary ebb in the flow of blood in the aorta.[9]

The large pulse pressure and this roughened aortic murmur may lead to the erroneous diagnosis of aortic valve regurgitation. It should be remembered that bradycardia, for reasons mentioned, may give the same two signs, especially in the older patient with aortic arteriosclerosis.

The elevated systolic pressure in bradycardia should not be mistaken for essential hypertension. Essential hypertension is not merely systolic hypertension but primarily a diastolic hypertension. In bradycardia the elevated systolic pressure is associated with a lowered diastolic pressure.

Finally a few remarks about irregular heart action. In the ordinary case of auricular fibrillation with irregular pulse action the systolic and diastolic pressures are quite uneven from beat to beat. Actual re-

cording with the Hamilton manometer shows variations of as much as 50 mm Hg between successive beats.[10] In such instances it is difficult to get the actual blood pressure level.

When we consider irregular heart action we must realize we are dealing with an average rate, some beats are faster, others are slower than the average. At slow rates this irregularity has little significant effect but at faster rates it makes a real difference. Take the case of auricular fibrillation with an average ventricular rate of 130, actually some beats are occurring at the rate of about 80 and other beats are close to 180. The beats at the fast rates have all the disadvantages enumerated in tachycardia and so cut down the effectiveness of the heart as a pump. It is to this, and not to the supposed lack of the auricular contribution, that one must attribute the fact that auricular fibrillation is less effective than sinus rhythm. This is demonstrated by the ineffectiveness of some beats which give rise to the well known pulse deficit in auricular fibrillation. The difference between a patient with a heart rate of 130 and regular rhythm and one with the same rate and auricular fibrillation is the irregularity in the latter, the fact that many of the beats occur in quick succession, that some of them are ineffective and do not even get to the wrist. It is on this basis that auricular fibrillation with rapid ventricular rate can cause aggravation of heart failure and act as the trigger to angina pectoris.

In conclusion, it is obvious that cardiac arrhythmias constitute an important chapter of cardiology, the understanding of which will not only lead to satisfaction to the student of clinical medicine but, more important, to an improved management of the patient.

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The list of "Recent Accessions to the Library" which has hitherto been published in the *Bulletin of The New York Academy of Medicine* will cease to appear there hereafter. Instead, it will be issued in mimeographed form and will be available to Fellows of the Academy and to other libraries on request. Applications to be placed on its mailing-list should be made to the Librarian.

PRESENT STATE OF KNOWLEDGE CONCERNING PATHOGENESIS AND TREATMENT OF RHEUMATIC FEVER*

MACLYN MCCARTY

It is not out of place to preface a discussion of the pathogenesis and treatment of rheumatic fever with a reminder of certain attributes of the disease which have an important bearing on investigations carried out in this field. Rheumatic fever is not one of those clear-cut syndromes, characterized by a group of uniform manifestations which are reproduced from case to case within relatively narrow limits. On the contrary, it is a highly variable disease. This variability has both qualitative and quantitative expression, since the manifold signs and symptoms can occur in numerous combinations and with a wide range of intensities. These facts, together with the further fact that there is no specific diagnostic test for the disease, lead to uncertainties in its recognition and make it impossible to describe a "normal pattern" to aid in the evaluation of therapeutic experiments. From the point of view of diagnosis, in investigative work it has been necessary to set up certain minimal criteria such as those advanced by Jones.[1] Although the use of criteria of this sort undoubtedly increases the chance that all cases in a given group under study actually have rheumatic fever, it must be realized that a large number of cases which have less well defined manifestations are summarily eliminated from consideration. For example, on the basis of the incidence of typical rheumatic heart disease among individuals giving no history of rheumatic fever, it would appear that the disease occurs frequently in a form so mild or atypical that it is unrecognized. This is hardly surprising in view of the fact that the disease, even when readily diagnosable on the basis of criteria such as those mentioned, may vary from a completely benign, brief illness without sequelae or residual cardiac damage to a prolonged debilitating illness of many months' duration or to a fulminating, rapidly fatal disease. This sketchy review merely touches on the problems arising from the protean nature of the disease but will serve to indicate that on this basis alone there is adequate ex-

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planation for the widely differing opinions that are held concerning the nature of rheumatic fever.

In considering the present state of knowledge of the pathogenesis of rheumatic fever, the concept of the mechanism of the disease that appears to be most widely held at the present time will be used as a framework for the discussion. According to this concept, the initial event in the disease is a hemolytic streptococcal infection of the upper respiratory tract. This infection in turn initiates a series of events, involving the action of streptococcal products and the complex host reaction to the streptococcus and its products, leading ultimately to the clinically manifest disease, which may occur and be perpetuated in the absence of demonstrable streptococci. The interactions between host and parasite, or its products, which result in the typical lesions of the disease are thought to involve antigen-antibody mechanisms. Obviously, this is no more than a skeleton scheme and leaves large gaps where real understanding of the mechanism is lacking. The closing of these gaps involves fundamental work in many different fields of medical science and an attempt will be made to illustrate the diversity of the current investigations which are in some way related to the problem of the pathogenesis of rheumatic fever. However, the present discussion will not provide a comprehensive review of all phases of the work on this disease.

The fact that infection by group A hemolytic streptococci is a preliminary to the development of acute rheumatic fever has been well established as the result of a number of epidemiological and immunological studies and more recently by clinical studies of prophylaxis with the aid of antibacterial drugs. The evidence for the importance of the streptococcus is sufficiently compelling so that it has gained wide acceptance, and it is unnecessary to review it here. A more important and debatable point, perhaps, is the issue of whether rheumatic fever is *invariably* preceded by a streptococcal infection. The answer to this question assumes importance in its effect on the direction and emphasis of investigative work. Obviously if the streptococcal infection is an obligatory component of rheumatic fever, it can be inferred that there is something unique about this organism, and the study of the components of the streptococcal cell should, if anything, be intensified. On the other hand, if streptococci represent only one of several different agents which can lead to the disease, the present emphasis on the detailed investigation of the streptococcal cell is probably misplaced.

Admittedly this is an extremely difficult question and there appears

to be no unequivocal answer possible at the present time. However, in view of the fact that the vast majority of cases of rheumatic fever can be shown to have been preceded by streptococcal infections, it is necessary to scrutinize with great care all claims regarding the initiation of the disease by other agents. Certain papers have been cited as providing evidence that rheumatic fever can be preceded by events such as traumatic injury, malaria, dysentery, vaccination against smallpox, etc.[2-5] For the most part these reports are characterized by the absence of any attempt to determine by bacteriological and immunological techniques whether a streptococcal infection has occurred in addition to the disease considered to have been the precipitating factor. Thus, much of their validity as evidence for a non-streptococcal etiology is lost. The evidence for a precursory streptococcal infection is not always easily obtained. In the first place, one must contend with the fact that the delay between an established streptococcal infection and the onset of rheumatic fever is frequently so long that the organism has disappeared from the throat and is not recoverable on culture. Furthermore, the absence of a demonstrable rise in one anti-streptococcal antibody – such as antistreptolysin O – is not important evidence against the occurrence of a recent streptococcal infection, since only 70-80 per cent of individuals with proved streptococcal infections have a significant antibody response to this streptococcal product. It has been emphasized that the chance of determining by immunological techniques whether a recent streptococcal infection has occurred is enhanced by increasing the number of different anti-streptococcal antibodies that are measured.

In addition to a deficiency of information concerning the occurrence of streptococcal infection in those cases of rheumatic fever which have been ascribed to other initiating agents, there are other factors that influence the interpretation of the data presented. For example, it is imperative to distinguish sharply between true *recurrences* of rheumatic fever and those *recrudescences* of activity that are common in chronic and polycyclic forms of the disease. In the latter case, many stimuli can apparently give rise to accentuation of rheumatic activity which had remained smouldering and subclinical for weeks, but these events are not comparable with the initiation of a new attack of the disease.

It must be apparent that the prejudices of the writer are on the side favoring the specific role of the streptococcus in the initiation of rheumatic fever. While none of the data supporting this point of view can be considered crucial, the evidence from many laboratories in which

multiple antibody studies have been carried out points in this direction. As an example of one approach to the problem, the antibody response of patients who develop rheumatic fever after known streptococcal infections can be compared with that of patients who are first seen with the symptoms of rheumatic fever, so that the occurrence of antecedent respiratory disease is uncertain. Thus, in a series of twenty-three cases of rheumatic fever following scarlet fever,[6] occurring in an epidemic at a naval training station during the last war, 83 per cent showed significant rises in antistreptolysin O; and an almost identical result (84 per cent) was obtained in a similar series of thirty-eight cases developing rheumatic fever after scarlet fever or streptococcal sore throat studied by Rothbard, Watson, Swift and Wilson at The Rockefeller Institute Hospital.[7] It is of interest to compare these results with our experiences in recent years with a group of patients admitted solely on the basis of the clinical picture of acute rheumatic fever. These cases are typical of the sporadic form of the disease as it occurs in civilian life. They were seen in all seasons of the year but with a peak incidence in the late winter and early spring. Less than half of the 45 patients of this series had positive cultures for group A streptococci at the time of admission, and in many instances the organism was present only in very small numbers. Furthermore, an even smaller number of these patients gave clear-cut histories of a preceding sore throat. However, as in the case of other groups just mentioned, 82 per cent showed a significant rise in antistreptolysin O. It is important to point out that all of these cases were examples of early acute rheumatic fever and similar results could not be expected if chronic cases of long standing were included. Antibodies to streptococcal products behave like most other antibodies in that they reach their maximum levels within a few weeks of the infection and then, in the absence of further antigenic stimulus, decline.

The similarity of the antistreptolysin O response of the group of sporadic cases to that of the group of naval trainees who developed rheumatic fever following scarlet fever can be further illustrated by comparing the rise and fall of the antibody titers with time. The mean antibody titers of these two groups relative to the onset of clinically manifest rheumatic fever are illustrated in Figure 1. In the cases of the scarlet fever group (upper curve), sera were available from the time of admission for scarlet fever and the progressive rise of antibody prior to the onset of rheumatic fever is apparent. These data as originally presented[6] were plotted only in relation to the onset of scarlet fever, but

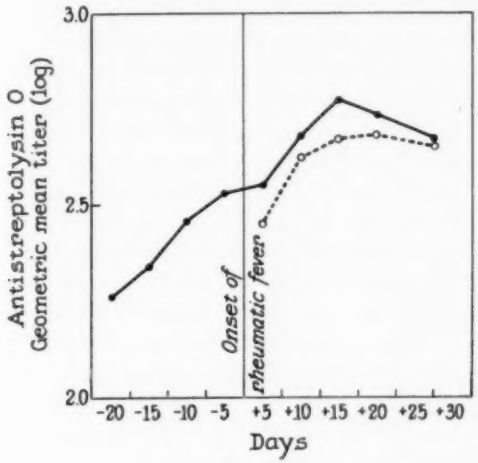

Fig. 1

in order to provide a basis for comparison with the group of sporadic cases (lower curve) the time of onset of the first rheumatic symptoms was used as the point of reference. The data on the forty-five cases of sporadic rheumatic fever begin only after this point of reference since none of these patients were seen until after the onset of the disease. However, the mean titer shows a rising curve parallel to and closely approximating that of the scarlet fever group, and considering the heterogeneity of this group of patients the curves of the two groups are remarkably similar. It would appear, therefore, that the pattern of antistreptolysin O response of a group of random cases of rheumatic fever is essentially identical with that of patients who develop the disease following a known epidemic of streptococcal infection.

It is possible that what is unique about the streptococcus is the fact that, due to the multiplicity of serological types, repeated infections with this organism are common throughout the age period when rheumatic fever has its highest incidence; and there are workers who have been impressed with the importance of the factor of reinfection with streptococci in the pathogenesis of rheumatic fever. However, it is difficult to believe that this is the sole attribute of hemolytic streptococci concerned with the initiation of this disease, and indeed studies on the biology of the streptococcus have demonstrated that the organism is

richly endowed with biologically active products which are worthy of special attention as possible participants in pathologic processes. The fact that a larger number of extracellular products, characterized either as toxins or as enzymes, is known in the case of group A streptococci than for any other organism may be only a reflection of the more widespread and intensive attention which streptococci have received; but it cannot be denied that certain of the streptococcal products are endowed with unusual interest.

As an example, streptokinase (or streptococcal fibrinolysin) is one of the streptococcal products which, since its original discovery by Tillett,[8] has been implicated on theoretical grounds as a possible factor in the sequelae of streptococcal infections. It is rather extraordinary that a bacterial product should possess the property of activating plasminogen, the precursor of a proteolytic enzyme present in mammalian sera; and furthermore that it should have a high degree of relative specificity for human plasminogen. Streptokinase is by far the most effective activator of human plasminogen that is known, and presumably, since it is active in very low concentrations, it is a potential factor in vivo during the course of streptococcal infection. However, there is no clear evidence at present to indicate that activation of plasminogen and the resultant release of free proteolytic enzyme in the blood is an important event in the evolution of rheumatic fever. Evidence of this type is difficult to obtain, and the question of the role of streptokinase remains open.

Among the extracellular products of streptococci there are others with properties which have directed attention to their possible participation in the pathogenesis of rheumatic fever. It was shown by Bernheimer and Cantoni,[9] for example, that streptolysin O, in addition to its well known hemolytic action on mammalian red cells, has a toxic effect on the isolated frog's heart. While the extension of this finding to the postulation of a cardiotoxic action in the human patient with streptococcal disease cannot be made, this represents a line of investigation that cannot be entirely neglected.

Streptococcal hyaluronidase is another of the extracellular enzymes which has attracted attention recently. The theoretical basis for this interest lies in the fact that, since rheumatic fever appears to be a disease of connective tissues, the elaboration of an enzyme which attacks one of the major constituents of the ground substance might well be of importance in the genesis of lesions. Unfortunately here again definitive evidence of any specific relationship to the evolution of disease processes

is lacking. The consideration of streptococcal hyaluronidase presents a special problem which may be of significance in the subtle interplay between host and parasite in streptococcal infections. Only a small minority of strains of group A streptococci produce appreciable quantities of hyaluronidase when cultured in vitro regardless of the medium employed. However, there is ample indication from studies of the specific antibody response to this enzyme that most strains must elaborate it under the conditions that obtain in tissues during active infection. The proportion of patients who respond with increased antihyaluronidase titers following streptococcal infections is as great as, or greater than, the proportion who form antistreptolysin O. It is difficult to avoid the conclusion, therefore, that the host provides a special environment for streptococcal cells with regard to the production or activation of hyaluronidase.

In addition to the extracellular streptococcal products just mentioned, there are several others known and almost certainly still others not yet identified. Furthermore, the streptococcal cell itself possesses an undetermined number of constituents among which there may be one or more of special importance in the induction of delayed effects of streptococcal infection. It is apparent, therefore, that streptococci do not suffer from any lack of potential agents for the initiation of pathological processes. The real lack is one of information concerning the various substances and their specific relationship to the events leading to the lesions of rheumatic fever. One must conclude at present there is no proof that any of the known components of group A streptococci are specifically involved in the development of rheumatic fever.

It has been shown, however, that several of these products are capable of inducing individually specific antibody responses following natural infections. This assumes significance in the light of the concept that antigen-antibody mechanisms are involved in the pathogenesis of rheumatic lesions. This concept, like the concept of the initiating streptococcal infection, evolved over a period of years as the result of more than one line of investigation. There are two types of information which are most frequently cited as implicating antigen-antibody mechanisms in this disease. First, there is the clinical observation that the latent period between the streptococcal infection and the onset of rheumatic fever, like the latent interval in serum sickness, coincides roughly with the period required for the appearance of large amounts of circulating antibody. Secondly, there are many experimental studies showing that lesions resembling to varying degrees those found in rheumatic

fever can be induced in laboratory animals by certain techniques of producing in vivo antigen-antibody reactions. To this type of evidence may be added the fact, now increasingly appreciated, that patients who develop rheumatic fever have on the average a quantitatively greater antibody response to the various streptococcal antigens than do patients who do not develop this sequela of their streptococcal infection. While it must be emphasized that this does not mean that every rheumatic individual develops higher antibody titers to the antigens studied than do non-rheumatic individuals, the finding nevertheless gives some support to the concept that "immune" reactions are involved in the disease. Furthermore, similar support is derived from the finding that penicillin treatment of streptococcal infections both depresses the antibody response and reduces the incidence of rheumatic fever.

If the antigen-antibody theory is accepted, one is still faced with a number of difficult problems other than the primary one concerning the nature of the antigen or antigens involved. For example, it may be asked: what is responsible for the localization of the injury resulting from the antigen-antibody reaction; what is the mechanism by which an antigen-antibody reaction can give rise to damage so severe as to result in permanent malformation such as occurs in the valves of the heart; and how does one explain the clinical observation that rheumatic activity can be perpetuated in some cases for many months in the absence of the initiating streptococcus which is the presumed source of antigen? There are no final answers to those questions, but certain current investigations have a bearing on the problems outlined.

In connection with the problem of the localization of the injury in rheumatic fever, a revision of some of the classical views may be necessary. It has been customary to classify rheumatic fever as one of the "collagen diseases" and thus to group it with a number of other diseases which are characterized pathologically by alterations in the connective tissue. However, some confusion has arisen from the fact that the term "collagen" used in a rather general sense in referring to the ground substance of connective tissue has been equated with the same term applied to a specific protein component of this tissue. Largely on the basis of histological staining reactions which have little claim to specificity, the fibrinoid material observed in the lesions of rheumatic fever has been considered to represent altered or degenerated collagen; and, as a result of these observations, the view has been advanced that the protein, collagen, is the initial site of injury. There are recent studies which

indicate that these assumptions are not tenable. G. E. Murphy[10] has carried out a careful and extensive histological study of the genesis of the typical Aschoff body of the myocardium. He has obtained convincing evidence that the fibrinoid material in the center of this lesion is not collagenous in character, as commonly supposed, but represents necrotic or degenerating myofibers. Similar evidence with regard to the collagenous origin of fibrinoid has been obtained in the case of the subcutaneous nodule of rheumatoid arthritis in a biochemical study carried out by Ziff and his co-workers.[11] By employing techniques which were developed for the quantitative determination of hydroxyproline, an amino acid which is present in large amounts in collagen, these workers were able to show that the fibrinoid material extracted from excised subcutaneous nodules contains no more than traces of this amino acid. On the basis of this finding and additional evidence such as the resistance of fibrinoid to collagenase and its susceptibility to tryptic digestion, it is concluded that the fibrinoid material is probably not derived from collagen. It is apparent that the problem of the initial site of injury in rheumatic fever cannot be considered settled.

The classical reactions of immunology, such as the Arthus and tuberculin reactions, have been used as models in studying the mechanism of tissue damage by possible antigen-antibody reactions in rheumatic fever, but fundamental knowledge of the basic processes involved in these reactions is itself too deficient for their study to be immediately helpful. The value of the further elucidation of the chain of events involved in these experimental phenomena is illustrated by recent studies by Stetson.[12-16] In a combined biochemical, histological and hematological investigation of the Shwartzman phenomenon he developed a coordinated concept of the pathogenesis of this type of tissue reactivity.[12-14] In extending these studies, he was able to show that the Arthus reaction in the skin of rabbits, in addition to its known histological similarity to the Shwartzman phenomenon, appears to have a similar mechanism operating in the development of the lesion.[15] Time does not permit a detailed discussion of the factors involved, and it will suffice to point out that a prominent feature of both reactions is the occurrence of leukocyte-platelet thrombi in a high percentage of the capillaries and venules of the involved skin areas. In a preliminary attempt to determine whether this type of thrombosis occurs in rheumatic disease, Stetson found leukocyte-platelet thrombi of the same characteristic appearance in the myocardium of autopsy specimens from patients dying

with rheumatic fever.[16] The thrombi were found only when other evidence of active rheumatic carditis, such as fresh Aschoff bodies, was present, and were found in none of the hearts of individuals dying from a variety of other diseases. No conclusion as to the significance of these observations is possible at this early stage, but the study represents an entering wedge and illustrates again the value of detailed investigation of laboratory models. Since in vivo antigen-antibody reactions appear to initiate this leukocyte-platelet phenomenon, Stetson's observations are susceptible to incorporation into any theory of the mechanism by which immunological reactions could result in the lesions of rheumatic fever.

The problem of the persistence of rheumatic activity, often for many months, in the absence of demonstrable streptococci is one of the most difficult aspects of the disease to reconcile with the streptococcal theory of etiology. Certainly, an explanation for this fact must be incorporated in any scheme purporting to outline the sequence of events in this disease. It has been commonly explained on the basis of the persistence of streptococci in hidden foci at a time when they are no longer demonstrable by throat or nasopharyngeal culture, but this explanation loses much of its appeal now that highly effective antibacterial agents have become available and have been shown to be without effect on the course of rheumatic fever, once the disease is established. Further evidence against the importance of foci of streptococci is provided by immunological data, since cases of persistent rheumatic fever have been observed in which there is a progressive fall in the titer of antibodies to streptococcal products. A bacterial focus which is active enough to perpetuate the rheumatic process would be expected to supply at the same time a continued antigenic stimulus and thus retard the fall of circulating antibody levels.

There are, of course, alternative explanations for the perpetuation of rheumatic activity in the absence of the hemolytic streptococcus. Indeed, the major basis for the ever-recurring thesis that the disease is caused by a virus-like agent, perhaps specifically provoked by the preceding streptococcal infection, appears to be that it would provide an adequate answer to this problem. However, there is little convincing evidence that such a virus exists. The theory that auto-antibodies to damaged host tissue are involved in the pathogenesis of rheumatic fever could also fit the pattern described, if one assumes that the auto-antibodies are capable of causing further tissue damage, leading again to auto-antigenicity. Unfortunately, after a promising impetus, the auto-anti-

body theory has not been supported by recent investigations.

Still another possible solution has been suggested by recent studies concerned with the persistence of antigen in host tissues. The work of McMaster,[17] for example, makes it quite clear that under certain conditions a foreign protein can remain in the tissues of the laboratory mouse for long periods of time. Since this phenomenon depends on the nature of the protein, with bovine serum albumin disappearing much more rapidly than bovine gamma globulin, it is conceivable that certain streptococcal products may possess unique properties that allow prolonged residence in human tissues. Against this concept, however, suggestive evidence is provided by the experimental work that long persistence of an antigen is dependent on a failure of the host to respond by antibody formation. Thus, when antibody is formed, the elimination of the antigen is rapid. If antigen-antibody mechanisms are in fact involved in rheumatic fever, it is not helpful to postulate the persistence of a non-antigenic streptococcal substance.

Other speculative solutions to the problem of the perpetuation of the disease process could be offered, but this seems fruitless in the absence of supporting evidence, and it is necessary to include this problem with the other unsolved aspects of the pathogenesis of rheumatic fever. It is evident that much remains to be learned of the details of the interactions between host and parasite which result in acute rheumatic fever before any well organized concept of the disease can be formulated. The great promise of the many attempts to produce rheumatic fever in laboratory animals lies not in the mere production of rheumatic-like lesions but in the possible development of a reproducible technique of producing a laboratory disease which can be considered wholly analogous to human rheumatic fever. With a model of this type, the possibility of tackling many of the riddles of pathogenesis will be greatly enhanced.

In view of the rather unsatisfactory state of the present knowledge of disease mechanisms in rheumatic fever, it would be pleasant to report that a more favorable situation exists in the practical problem of treatment of the disease. Unfortunately, the present status of treatment is only slightly more satisfactory. Most clinicians agree concerning the importance of conservative management in the general care of rheumatic patients, but when one reaches the realm of specific therapy one finds less unanimity as well as an inadequate basis for reaching conclusions. It is important to remember in this connection that, although salicylates have been used in this disease for many decades and have enjoyed the

reputation of being a specific anti-rheumatic agent, differences of opinion concerning their value still exist, and no one has been able to establish conclusively what effect the administration of salicylates has on the development of permanent cardiac malformations. If one were to attempt a survey of the current opinion regarding salicylates, one would probably have to say that most workers believe that they are of value in controlling acute symptoms but that they do not prevent permanent cardiac damage.

To explain why a therapeutic agent, which has been as widely used in rheumatic fever as salicylate, has not been more accurately evaluated, it is only necessary to turn again to those characteristics of the disease that were mentioned earlier. It is not possible at the outset of an attack of rheumatic fever to predict how severe it will be, how long it will last or whether it will leave permanent cardiac damage in its wake. It is surprising how frequently patients with undoubted rheumatic fever will promptly get well with no treatment other than bed rest. On the other hand, there are those patients who remain serious therapeutic problems when all available treatments have been tried. This variability, together with the uncertainties of diagnosis and prognosis, have made it difficult to carry out clinical studies that are sufficiently extensive and well-controlled to provide definitive answers.

The present importance of these considerations lies in the fact that they will doubtless have the same effect on the evaluation of the therapeutic action of cortisone and adrenocorticotrophic hormone. A difference of opinion on the effects of these agents is already apparent in the published reports from various clinics. It is agreed that cortisone and adrenocorticotrophic hormone usually bring the signs and symptoms of rheumatic activity under control, perhaps more promptly than salicylates can, but whether the basic mechanisms of the disease are affected or permanent damage prevented cannot be concluded from the available data. There are grounds for believing that all these agents, salicylates and the hormones, achieve their effect by interference with the usual host response to the pathological process without affecting the underlying process itself. The rapid return of symptoms on withdrawal of therapy strongly suggests that this is true. However, this does not eliminate the possibility that interference with the host response might have a retarding influence on the development of the type of lesion that leads to permanent damage.

Because of the importance of finding answers to these questions, the

cooperative project involving many clinics in this country and in England and initiated by The American Council for Rheumatic Fever is of great interest. This is an attempt at a controlled, long-term therapeutic study on a scale sufficiently large to give more hope of a definite answer. It remains to be seen whether the vagaries of the disease will affect the drawing of final conclusions from the study.

The consideration of these new therapeutic agents brings up the possibility, not considered earlier in this discussion, that hormonal mechanisms play a special role in the pathogenesis of the disease. The success of symptomatic therapy with adrenocorticotrophic hormone and cortisone has led to the assumption that the adrenal gland is directly and crucially involved in the chain of events which starts with the streptococcal infection and ends with rheumatic fever. However, except in the general sense that the adrenals, along with many other organs, are involved in the host response in disease, this does not appear to be a very fruitful assumption. On the contrary, the effect of these agents in various other conditions greatly reduces the likelihood of any specific relationship between adrenal mechanisms and rheumatic fever. For example, the fact that administration of adrenocorticotrophic hormone will bring about practically complete disappearance of the symptoms and gross lesions of tuberculous laryngitis or will suppress the overt manifestations of pneumococcal pneumonia hardly provides evidence that adrenal mechanisms are involved in the pathogenesis of these diseases. Rather this would appear to mean that many of the symptoms of disease depend upon the nature of the host reaction to the pathogenic agent and this reaction is partially, at least, under hormonal control so that it is altered artificially by an excess of certain adrenal hormones. The host reaction is limited to a relatively few patterns and may not possess the versatility required to be uniformly beneficial in response to all varieties of pathogenic processes; but it is still probable that it is oriented toward ultimate control of the process and may be beneficial despite the fact that it contributes to the symptoms of disease.

In concluding this discussion, since a summary of the diverse topics presented is not feasible, it can only be repeated that the study of rheumatic fever is currently in that stage of development characterized by numerous hypotheses and a wealth of apparently unrelated observations. While many of the past advances have been consolidated in recent years, coordination and synthesis of the new information will be possible only when additional facts become available.

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THE EPIDEMIOLOGY AND PREVENTION OF RHEUMATIC FEVER*

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ALTHOUGH reports concerning the epidemiology of acute rheumatic fever are legion, the conclusions reached by various investigators are frequently contradictory. Various environmental, bacterial and host factors have been studied in relation to the occurrence of this disease. It is well established that the incidence of rheumatic fever may vary from year to year in the same population groups. Occasionally, the epidemic occurrence of the disease is noted. In general, rheumatic fever is most prevalent during the winter and spring months at a time when respiratory infections reach their maximum incidence. Although the disease occurs frequently in the temperate zones, it cannot be said to be rare in all tropical areas. In this country, rheumatic fever is noted for its high incidence along the northern Atlantic sea coast among population groups living under crowded, damp conditions and under poor economic circumstances. In contrast to this environmental status, are the conditions that prevail in another portion of the country, the Rocky Mountain states. Here, at a high altitude, under conditions of low humidity and less concentration of the population units, the incidence of rheumatic disease is about equal to that observed along the northern Atlantic coast.

Many studies concerning the epidemiology of rheumatic fever fail to consider the role of preceding respiratory illnesses. Some observers have felt that the clinical characteristics of this initial infection are important. It has been suggested that scarlet fever and superficial streptococcal infections are especially prone to precipitate an attack of rheumatic fever. Likewise, there are those who believe that certain

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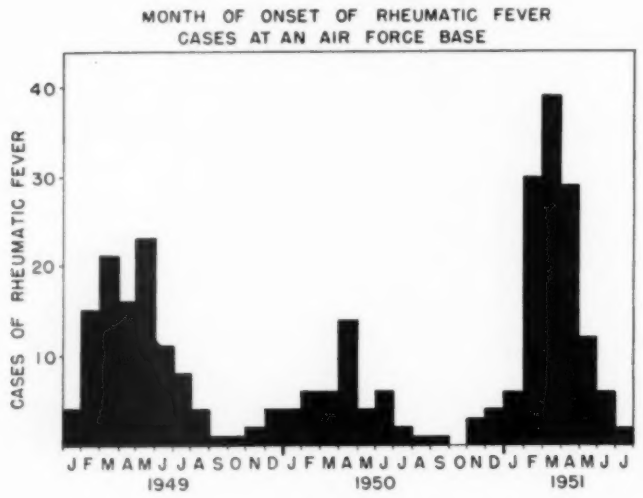
MONTH OF ONSET OF RHEUMATIC FEVER
CASES AT AN AIR FORCE BASE
CASES OF RHEUMATIC FEVER
40
30
20
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J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J
1949
1950
1951

Fig. 1

strains or serological types of streptococci are more rheumatogenic than others.

Rheumatic fever is said to be a disease of children, and yet there have been numerous reports of its occurrence in adults. Because of the high incidence among the younger age groups it has been assumed that age alters the susceptibility to acute rheumatic fever, however, statistical evidence in support of this assumption is lacking.

That some factor in the host may be important in the pathogenesis of rheumatic fever is evident from the high attack rates observed in the offspring of rheumatic parents and also the increased susceptibility conferred by a previous attack of the disease.

The role of these environmental, bacterial and host factors which have been summarized briefly is difficult to assess, primarily because of the inadequacies of methods for diagnosis and lack of agreement among physicians as to the cause of rheumatic fever. Since the evidence now available indicates that infection with group A streptococci is causally related to the disease, the various epidemiological factors will be reviewed in order to define the role of such factors on either the incidence of streptococcal infections or on the incidence of rheumatic fever.

TABLE I.—RHEUMATIC FEVER ATTACK RATES BY YEAR

Year	*Exudative Tonsillitis*	*Rheumatic Fever*	
		Number	*Per cent*
1949	573	14	2.4
1950	439	12	2.7
1951*	194	6	3.1

* Jan. to 15 Feb.

During the past three years the staff* of the Streptococcal Disease Laboratory has been interested in the study of streptococcal infections and acute rheumatic fever. One method employed in these studies has been the determination of the attack rates of rheumatic fever in well defined population units. In the studies to be presented here, the population unit includes airmen admitted to the hospital with exudative tonsillitis or pharyngitis from whom typeable group A streptococci were isolated. None of these patients received therapy with the antibacterial agents. In addition, only those patients who were observed at follow-up examination 21 or more days after the onset of the streptococcal infection are included. For purposes of tabulation rheumatic fever developing within 35 days of the streptococcal respiratory infection was considered a complication of that infection since it has been observed that patients developing rheumatic fever at a later date usually have had an intervening streptococcal infection.[1]

RESULTS

The occurrence of acute rheumatic fever over a three year period at Warren Air Force Base is shown in Figure 1. Only those patients developing rheumatic fever after arrival at Warren are shown. These data emphasize the differences in the epidemic pattern during three different years as well as the seasonal variation in the appearance of acute rheumatic fever. The winter and spring months were associated with the highest incidence of rheumatic fever and this was also the period when most streptococcal and other respiratory infections were observed.

Data such as shown in Figure 1 have been presented many times,

* These data could not have been obtained without the interest and support of Doctors William R. Brink, George C. Eckhardt, Edward O. Hahn, and Harold B. Houser who were members of the professional staff some time during the period of this study.

TABLE II.—RHEUMATIC FEVER ATTACK RATES BY SEASON

Year	Months	Exudative Tonsillitis	Rheumatic Fever	
			Number	Per cent
1949	Jan.-June	451	12	2.7
	July-Dec.	122	2	1.6
1950	Jan.-June	333	8	2.4
	July-Dec.	106	4	3.8

TABLE III.—RHEUMATIC FEVER ATTACK RATES BY SEASON (1949-1950)

Months	Exudative Tonsillitis	Rheumatic Fever	
		Number	Per cent
Jan.-June	784	20	2.6
July-Dec.	228	6	2.6

but they fail to define the factors responsible for these variations. The data presented in Table I show that the attack rate for rheumatic fever as based on population units known to have had a streptococcal infection was relatively constant throughout the period of study. In Table II the data are presented according to season. During the winter months of 1949 and 1950 the attack rates varied little, but during the summer and fall the attack rate in 1949 was 1.6 and in 1950 was 3.8 per 100 streptococcal infections. These latter variations are probably due to the small number of infections included in the summer and fall months. If the experience during the two years is combined (Table III), the attack rate is constant and is independent of the season. These data indicate that the effect of season and year on the incidence of rheumatic fever is related to the effect of such factors on the incidence of the preceding streptococcal illness.

It is commonly believed that rheumatic fever occurs less frequently in certain geographical areas than in others.[2] That this variation may be due to factors which influence the incidence of streptococcal infection is indicated by the data presented in Table IV. Unfortunately, few follow-up studies have been made after defined infections, but it is believed that the populations included in Table IV are relatively comparable in that most of the infections were probably streptococcal

TABLE IV.—RHEUMATIC FEVER ATTACK RATES BY GEOGRAPHICAL AREAS

Location	*Year*	*Type*	*Streptococcal Infections*	*Rheumatic Fever*	
				Number	*Per cent*
North Carolina (3)	1943	5	100	3	3.0
Wyoming	1949-51	5	234	7	3.0
Denmark (4)	1926	—	840	30	3.6
Boston (5)	1950	—	102	4	3.9

in origin, and it was stated by the author that all patients were followed for complications.

The incidence of rheumatic fever following streptococcal infections appears to be constant in North Carolina[3] and Wyoming. Both of these studies were conducted in a similar manner and included only young adult males infected with type 5 streptococci. One was at a high altitude (over 6,100 ft.), the other at a low altitude (under 200 ft.). The study in Denmark[4] was done on 840 patients reported to have septic sore throat. The authors believe that the attack rate of rheumatic fever may be somewhat high since there was a tendency to report a case of sore throat if a complication developed. The figures from Boston[5] were obtained in a group of scarlet fever patients observed for at least three weeks. The methods of observation and diagnosis in the latter investigation would tend to give higher rates than in the Wyoming and North Carolina studies.

These figures (Table IV) indicate relatively little direct effect of altitude, climate, or humidity on the attack rate of rheumatic fever. Further studies would be desirable, especially following proved streptococcal infections in tropical areas.

As stated previously, acute rheumatic fever is commonly believed to be a disease of the young. In Wilson's[2] series the average age of onset of rheumatic fever was about six to seven years, although it is recognized that the disease frequently occurs after the age of twenty-five.[6] The data concerning attack rates following known streptococcal infections according to the age of the individual are meager, but they fail to show that the young child is more susceptible to rheumatic fever than the adult (Table V). The data of Collins[7] have shown that the age of highest incidence of scarlet fever is six, suggesting that the

TABLE V.—RHEUMATIC FEVER ATTACK RATES BY AGE AND TYPE OF DISEASE

Description	*Sterptococcal Infections* *Type*	*Number*	*Rheumatic Fever* *Number*	*Per cent*
Male adults, average age 20 (Wyoming)	Air-borne Tonsillitis	1206	32	2.6
Children, average age 11 (Boston (5)	Air-borne Scarlet Fever	102	4	3.9
One-third under 15 (Denmark*)	Milk-borne Tonsillitis	92	3	3.3

* Henningsen, E. J. and Ernst, J. Milk epidemic of angina, originating from a cow with mastitis and due to Streptococcus pyogenes (Lancefield group A), *J. Hyg. 38*:384-91, 1938.

explanation for the high incidence of rheumatic fever in the young age group is due to the high incidence of streptococcal infections. It is of some interest to note that the attack rate for many respiratory infections is highest at about the age when the child first attends school, and is lowest in the adult.[7, 8]

It would seem reasonable to assume that the effect of crowding on the incidence of rheumatic fever is related to an increased incidence of streptococcal infections under such circumstances. Data supporting such an assumption are not conclusive, but it has been shown that the attack rate of other respiratory infections tends to increase as the size of the family unit increases.[9] In a study of Navy personnel Breese[10] has shown that the amount of respiratory disease is related to the number of individuals housed in a single unit. Certainly epidemics of rheumatic fever in the military organizations are usually associated with streptococcal infections among personnel living under crowded conditions.[11]

There is little evidence that the type of disease produced by the group A streptococcus alters the attack rate for acute rheumatic fever. The three groups of infections shown in Table V include an air-borne outbreak of tonsillitis and scarlet fever, and a milk-borne epidemic of septic sore throat. The attack rate in each instance was relatively comparable.

In contrast to these data are the reports of Watson, Rothbard and Swift[12] and Coburn and Young.[11] The former authors record that in a group of 110 patients with scarlet fever, eight patients subsequently developed clinical attacks of acute rheumatic fever, an attack rate of 7.3.

TABLE VI.—RHEUMATIC FEVER ATTACK RATES BY THE SEROLOGICAL TYPE OF STREPTOCOCCUS

Type	*Exudative Tonsillitis*	*Rheumatic Fever*	
		Number	*Per cent*
1	42	2	—
5	234	7	3.0
6	35	0	—
12	42	0	—
14	630	17	2.7
24	198	5	2.5

One of these cases of rheumatic fever would have been excluded in the studies at Wyoming because of the long latent period of forty days. Furthermore, two additional patients had such mild and transient symptoms that they would not have been discovered without very careful observation. In a group of 500 patients with scarlet fever in a Navy installation, Coburn and Young[11] state that there were 106 cases of rheumatic fever, however, no details are recorded. These authors note that there was a correlation between the attack rates of scarlet fever and rheumatic fever in various Navy installations, but it does not necessarily follow that strains of streptococci which produce scarlet fever are always associated with a high rheumatic fever incidence.

It is possible that the rheumatogenic capacity of various strains of streptococci vary. Thus, Coburn and Young[11] state that two outbreaks caused by types 1 and 12 streptococci failed to precipitate rheumatic fever, whereas in the 500 scarlet fever patients presumably infected with type 17 streptococci, 21 per cent developed this complication. To date the studies at the Streptococcal Disease Laboratory fail to show significant variations in the attack rate according to the type of streptococcus isolated from the preceding streptococcal illness (Table VI). Furthermore, there did not appear to be a difference in the attack rate early and late during the course of an epidemic due to a single type.[13]

There are several factors that appear to be related to an increased attack rate for rheumatic fever following streptococcal infections. These include a positive familial history, a previous attack of rheumatic fever, and an altered antibody response exhibited to the preceding streptococcal infection.

TABLE VII.—RHEUMATIC FEVER ATTACK RATES IN SUBJECTS WHO HAVE HAD RHEUMATIC FEVER

Author	*Sterptococcal Infections* *Type*	*Number*	*Rheumatic Fever* *Number*	*Per cent*
Kuttner[18]	C 51	12	6	50
	4	32	0	0
	97 T	6	0	0
	27	39	8	20.5
Schlesinger[17]		62	22	35.6
Coburn[19]	single type	16	14	87.5
Collis*		32	24	75
Coburn[20]		38	19	50

* Collis, W. R. F. Discussion on some problems concerning the prevention and treatment of acute rheumatic infection, *Proc. roy. Soc. Med.* 25:1631-35, 1932.

Attack rates for rheumatic fever following known streptococcal infections in individuals with a positive family history are not available for analysis. The observation of St. Lawrence[14] that 14.8 per cent of persons exposed to a patient with rheumatic heart disease within a family unit showed evidence of rheumatic fever or rheumatic heart disease suggests an increased susceptibility in such families or increased exposure to a rheumatogenic agent. Paul[15] in a study of 15 rheumatic families observed the simultaneous appearance of both primary and recurrent bouts of rheumatic fever. The studies of Wilson[2] and Gauld[16] have shown that the risk of rheumatic fever is greater in children of parents with a history of rheumatic fever than in children of parents who have not had the disease. These data indicate that heredity may be a factor in the determination of the attack rate of rheumatic fever.

There is little doubt that a previous attack of rheumatic fever usually increases the risk of recurrent attacks following a streptococcal infection.[17] Examples of rheumatic fever occurring after such infections are shown in Table VII. These data also show a remarkable variation in the attack rates, suggesting that certain strains or types of streptococci vary in their rheumatogenic capacity. The type 4 epidemic of Kuttner[18] appeared to have no rheumatogenic capacity. These infections apparently were typical clinical examples of streptococcal disease, although it is somewhat unusual that only eleven of the thirty-two patients showed a diagnostic increase in the antistreptolysin titer. Whether the failure

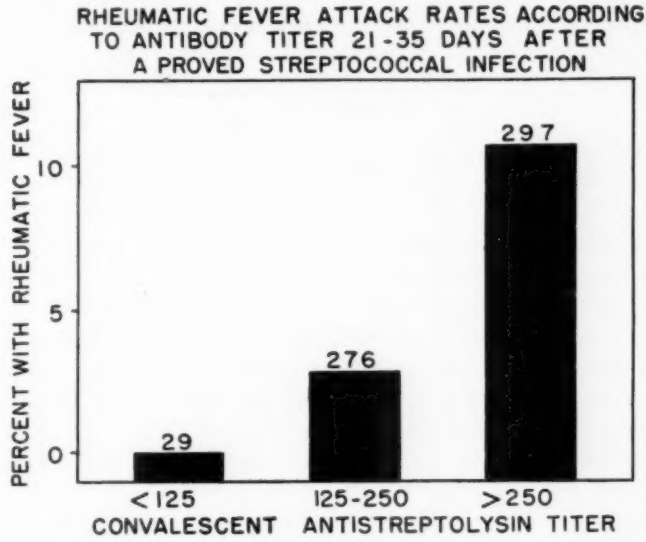

Fig. 2

of this type of streptococcus to induce rheumatic fever was related to its failure to produce an antibody response cannot be determined. It may be of interest to record that rheumatic fever has been observed to follow type 4 infections in Wyoming. Coburn[19, 20] made an interesting observation during a study of 20 strains of streptococci isolated from infections which were followed by rheumatic fever and 20 strains isolated from patients who did not experience such a sequela. Most of the strains from the latter group failed to produce streptolysin O in vitro.

Although the data in Table VII may be interpreted as showing variations in the rheumatogenic capacity of various strains of streptococci, it is difficult to be certain of this since there may be multiple factors altering the attack rates in such populations. For example, the chances of recurrence are related to the number of years of freedom from an attack of rheumatic fever.[21] Furthermore, if a streptococcal infection were defined as occurring only in those patients whose sera showed an antibody response, the attack rates might be comparable. It is apparent that further data are required in such population groups.

TABLE VIII.—RHEUMATIC FEVER DEVELOPING WITHIN 34 DAYS OF ONSET OF EXUDATIVE TONSILLITIS OR PHARYNGITIS

Treatment	*Exudative Tonsillitis*	*Rheumatic Fever*
None	996	23
Penicillin	978	1

For some years it has been recognized that patients developing rheumatic fever are especially likely to have high titers of antibody to various streptococcal antigens.[22,23] The correlation of the magnitude of the antibody response (antistreptolysin) with the attack rate for acute rheumatic fever is shown in Figure 2. All patients in this study harbored group A streptococci and were shown to develop a diagnostic increase in the antistreptolysin titer following the infection. In the group of 602 patients the attack rate increased as the height of the convalescent titer increased.

Methods established for the control of acute rheumatic fever have been based on the fact that there is a causal relationship between the acute streptococcal infection and the subsequent attack of rheumatism. Thus, the continuous exhibition of the sulfonamide drugs decreases the attack rate of streptococcal infections and rheumatic fever.[11] Such procedures are limited to selected population groups and include primarily individuals who have had a previous attack of rheumatic fever. Because of the relation between the magnitude of the attack rate and the height of the antibody response, it has been assumed that methods of therapy of the acute streptococcal infection which result in an inhibition of antibody formation might also reduce the attack rate of rheumatic fever. Three drugs, penicillin, aureomycin and terramycin are known to inhibit antibody production when administered to patients with streptococcal infections.[24] A summary of the results obtained when penicillin is administered to patients with streptococcal illnesses is shown in Table VIII. Early treatment resulted in a twenty-fold reduction in the incidence of rheumatic fever. The one patient who developed this sequela following therapy had had rheumatic fever and chorea one year previously and did not receive treatment with penicillin until the fifth day after the onset of tonsillitis. The results obtained with aureomycin therapy have been similar to those obtained with penicillin. These results

confirm the observations of Massell, Dow and Jones[25] who studied the effect of antibiotic therapy of streptococcal infections on the recurrence rate in rheumatic subjects.

Discussion

In summary, the study of the epidemiology of rheumatic fever has indicated that there are environmental, bacterial and host factors which play a role in the development of rheumatic fever. It would appear from the limited data presented, however, that many of these factors are important only because they are related to the preceding streptococcal infection which initiates the attack of rheumatic fever. Thus it seems likely that latitude, altitude, crowding, economic factors and age all affect the incidence of rheumatic fever only because they are related to the incidence of streptococcal infections in general. A better understanding of the mechanism of action of these factors on the incidence of streptococcal infections may lead to better methods for control of rheumatic fever.

The data indicate that host and bacterial factors are most important once a streptococcal infection is established. From the attack rates following streptococcal infections in the general population there is little evidence that the various serological types of streptococci vary in their rheumatogenic capacity, nor is there definitive evidence that the type of disease produced is an important factor in the attack rate of rheumatic fever.

Studies of rheumatic populations have shown marked variations in the attack rate for rheumatic fever following streptococcal disease. At the present time these data are difficult to interpret and considerable more information is required to determine the role of the streptococcus and the role of the host. It would appear, however, that both bacterial and host factors may be important in the altered attack rates observed.

In this group of rheumatics recent contact with the streptococcus also may play a role. It has been postulated that multiple streptococcal infections increase the attack rates for rheumatic fever,[26] and for this reason alone the previous rheumatic may be more susceptible than normal subjects to rheumatic fever. Data are now being obtained concerning attack rates following one and two observed streptococcal infections to assess the role of multiple infections. The fact that the attack rate for recurrent rheumatic fever falls as the interval of freedom from an attack

increases, indicates that repeated attacks of streptococcal infections may increase the attack rate.

Another explanation for the increased susceptibility of the rheumatic patient to subsequent attacks following a streptococcal infection is that such a population has a high degree of a "host factor." The data presented indicate that individuals who develop rheumatic fever respond in an altered fashion immunologically. This altered response again may be due to bacterial or host factors. Studies have been underway during the past three years to determine the relative importance of these two factors. Since there is evidence that there is a predisposition to increased antibody production,[27, 28] subjects with streptococcal infections are being tested with multiple antigens to determine the role of the infection and the role of host factors in the determination of the type of antibody response. It has been the working hypothesis that such immunological hyperreactivity may be responsible in a large part for the development of rheumatic fever, and also may be the inherited characteristic that accounts for the high attack rates in certain families.

To date, all successful methods for the prevention of rheumatic fever have been based on the knowledge of the relationship of group A streptococcal infections to the disease. Thus the prophylactic administration of antibacterial agents prevents most streptococcal infections and thereby prevents an attack of rheumatic fever. Such methods of control have been limited in their use almost completely to one population group, the previous rheumatic. The use of penicillin or aureomycin in the treatment of acute streptococcal infections as a preventive measure is likewise limited since approximately 40 to 50 per cent of individuals infected fail to develop sufficient clinical symptoms to require medical attention. It would appear that only by the control of all streptococcal infections can rheumatic fever be eradicated.

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TWENTY-FIFTH GRADUATE FORTNIGHT

October 6 to 17, 1952

HORMONES IN HEALTH AND DISEASE

Fellows of The New York Academy of Medicine will be furnished registration cards without application. For others, a registration card will be sent upon receipt of check for ten dollars, payable to The New York Academy of Medicine.

Medical officers of the armed services, in uniform, will be admitted without charge.

Interns and residents will be admitted without charge, provided they present letters from their chiefs of service. They will be seated as facilities permit, after Fellows of the Academy and other registrants have been accommodated.

THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street TRafalgar 6-8200

PRESENTATION OF PAUL EHRLICH MEMENTOS

On Wednesday, December 5th, 1951, there was presented to The New York Academy of Medicine a number of Paul Ehrlich Mementos. These comprised Ehrlich's microscope, his court uniform and ceremonial sword, and a death mask of Ehrlich. The Mementos were presented to the Academy by Ehrlich's daughter, Mrs. Ernest Schwerin, and her sons, Dr. Hans W. Schwerin, and Mr. Gunther K. Schwerin.

The presentation ceremony took place in the Rare Book Room, in the presence of a group of Academy Fellows and friends. The proceedings were opened by Dr. Wm. Barclay Parsons, President of the Academy, who, accepting the Mementos, responded to the presentation comments of Dr. Hans W. Schwerin.

Thereafter the gathering was addressed by Professor Selman A. Waksman and by Professor Perrin H. Long whose addresses follow.

HANS W. SCHWERIN

DR. PARSONS, Members of the Academy of Medicine and Ladies and Gentlemen:

It is a great pleasure to me to present to you this microscope which belonged to my grandfather, Paul Ehrlich, and which he used as a very dear and indispensable tool in his work. I can think of no worthier recipient for the Paul Ehrlich* memorabilia than The New York Academy of Medicine.

May I ask you to accept these mementos as a token of esteem for your great Institute that has become a "treasure chest" for the medical science. And may these mementos become inspiring stimuli for future generations.

* Paul Ehrlich was an Honorary Fellow of the Academy from February 4, 1904 until his death Aug. 20, 1915.

PAUL EHRLICH – AS MAN AND SCIENTIST*

SELMAN A. WAKSMAN, PH.D.

Professor of Microbiology, Rutgers University, New Brunswick, N. J.

PAUL EHRLICH is best known for his discovery of salvarsan (606) and as the father of chemotherapy. What is less known is the fact that he was a brilliant chemist, that he has made important contributions to our knowledge of bacteriology through his work on the staining of bacteria, and that he was one of the discoverers of the theory of immunology which has had such a profound influence on serotherapy and the use of antitoxins.

I never had the privilege of knowing Ehrlich personally, especially since he died in 1915, the year that I graduated from college. However, one of the first problems that engaged my attention after the completion of my doctorate work, dealt with the toxicity and effectiveness of salvarsan. Our entrance into the First World War and the great need for this drug which resulted from it led to the rapid development of its large scale production in this country. I became associated with one of the companies manufacturing it. It was my job to study its toxicity and other pharmacological properties in order to control its safe use. I became intensely interested in Ehrlich's work and became fascinated by his personality and by his method of scientific investigation.

Ehrlich was the first to lay emphasis upon the fact that the infecting agent may be more sensitive to treatment with chemical substances than the infected body cells. These ideas were quite contrary to the prevailing conception, as expressed by von Behring and by many others, that the host is usually poisoned more rapidly than the infecting germs by the action of chemical agents. Ehrlich's ideas pointed a way to sound and fundamental principles in the field of chemotherapy, which reached their particular heights with the discoveries of the sulfa drugs and antibiotics. Although it took a quarter of a century or more for these, rather than five or ten years as predicted by Ehrlich, they followed the path laid down by him.

* Address delivered December 5, 1951, at The New York Academy of Medicine on the occasion of the presentation of the Paul Ehrlich Mementos.

Paul Ehrlich was born in a small town in Silesia in 1854. His mother appeared to influence greatly his early education. In school, he was a brilliant scholar, some of his friends referring to him as a "Lernkopf." His extreme modesty prevented him, however, from asserting himself. He was particularly interested in ancient languages, in mathematics and in natural sciences. He was apparently not too fond of schoolwork, since he was always looking forward to his return to his "laboratory," a room in his parents' house, which he fixed up for chemical studies with dyes and for his biological collections.

At an early age, Ehrlich learned to combine theory with praxis. Thus his observations on the adsorption of methylene blue upon the nervous tissues led him to postulate the potential practical utilization of this reaction for disease control. The story is told that when he had to write an essay on "Life as a Dream," he described life as dependent upon normal oxidation processes, nerve activity being one such process; a dream is a form of oxidation, resulting in the phosphorescence of the brain. This scientific exposition by a mere youth of an idea where a poetic outburst was no doubt expected hardly satisfied his examiner.

Ehrlich became interested at an early age in the problem of staining tissues and cells. His cousin, Karl Weigert, somewhat older than he, who had already made an outstanding contribution to the staining of bacteria, served as a model for his future scientific development and aroused especially his interest in dyes.

As is usually customary for German students, Ehrlich studied medicine at several universities, namely in Breslau, Strassburg, and Leipzig. He received his M.D. from the latter in 1878. At Strassburg, Ehrlich came under the influence of the anatomist Waldeyer and at Breslau, under that of the pathologist Cohnheim, both of whom greatly admired his zeal and scientific interests. In his early experiments, he discovered a new variety of cells, "mast-cells." His Doctor's thesis dealt with the subject of "Chemical and histological staining principles using aniline dyes." The youthful scientist developed the idea of chemical reactions of heterogeneous substances with the cell protoplasm, which was later to lead to his famous side-chain theory. His experience in staining was made good use of in his first position as assistant in Charité Hospital in Berlin. The urine and blood preparations which Ehrlich made were soon to become famous. These were so well made that he could follow the course of disease, especially in the case of typhoid patients.

While listening to Robert Koch's famous announcement, made in

1882, of the discovery of the tubercle bacillus, Ehrlich remembered the rods which he usually saw in the sputum of tuberculosis patients. He joined Koch in the further elucidation of the problem of the etiology of this disease. This was the beginning of Ehrlich's interest in bacteriology.

Ehrlich was often spoken of as a "born chemist." Only by combining a medical training, an appreciation of biological reactions with chemical perspicacity, was he able to obtain a profound insight into the problems of disease, of body immunity and of chemotherapy, which laid the foundation for the new science of the nature and control of infectious diseases.

His early interests in staining techniques led him to a study of the distribution of dyestuffs in the animal body. As a result of these studies, he was able to differentiate and classify various types of body cells, particularly the blood leukocytes. This was followed by studies of vital staining, whereby the various dyes were found to be specific in their staining capacity of different organs or cells. As a result of these and other studies, Ehrlich concluded that "the ways and means by which drugs are distributed through the body must be of the greatest importance in the rational development of therapeutics."

In 1887, Ehrlich himself contracted tuberculosis. This forced him to leave for Egypt where he spent the next two years. Upon his return he continued his collaboration with Koch. He also helped von Behring in his work on diphtheria antitoxin. Unfortunately, the last collaboration ended disastrously, because of the personality of von Behring, who did not give Ehrlich sufficient credit for his important contribution, which alone made possible the large-scale production and practical utilization of antitoxins. He also introduced standards for measuring the potency of antitoxins and defined the units of their activity.

Ehrlich not only established the principles fundamental to the measurement of activity of biological agents, but he also elucidated the nature of the reaction whereby the body becomes immune to further infection. The formation of antibodies, or substances which tend to neutralize the infective agent or poison, was thereby recognized as the important mechanism with which the body tends to combat disease. Immunology and allergy are greatly indebted to Ehrlich's fundamental work.

Thus began, on the part of Ehrlich, a search for substances which would combine and destroy, neutralize, or weaken the infecting organism without injuring the patient. He first tested, in 1891, the possi-

bilities of methylene blue in the treatment of malaria. In 1902, with experimental animals at his disposal, he began to develop the field of "chemotherapy," which led to the discovery of chemical substances which would have a harmful effect upon the infecting parasite without injuring the host. Ehrlich made a sharp differentiation between the "parasitotropic" and the "organtropic" effect of antimicrobial agents. He recognized the fact that serum therapy is not effective in all infectious diseases, notably those caused by protozoa and protozoan-like organisms. His future discoveries were, therefore, directed largely upon the latter.

Ehrlich was appointed as Director of the State Institute for the Control of Sera at Steglitz and later at Frankfurt. He was soon made Director of the Serum Institute, where he made his classical contributions to immunotherapy and where he developed his ideas on the "side-chain" theory of immunity. Finally, he became Director of the Georg Speyer-House, where he was to spend the rest of his life.

In 1884, Ehrlich was made a titular professor, without being proposed, however, to a University Chair for fifteen years. Between 1877 and 1914, he published 232 scientific papers and books. In addition there were published more than 400 papers by his assistants and collaborators.

His first experiments in chemotherapy were made in 1891. This was a result of his work with dyes and vital staining. The discovery that methylene blue stained the malarial parasite led him to try the effect of this dye on malarial patients. Some patients benefited by such treatment. Although the results were not conclusive, they led later to the discovery by others of the important antimalarial drugs atebrin and plasmoquin.

Ehrlich's important contribution to immunology was published in 1897. His work on the fixation of oxygen by certain groupings in the protoplasm led him to the idea of the presence in the protoplasm of numerous other "receptors," whereby various foodstuffs are anchored prior to their incorporation in the cell. The toxins and antigens also combined with specific receptors of the cell; the latter was thus forced to replace the receptors by new ones in excess; these finally broke off and found their way into the blood, thus serving as specific antitoxins or antibodies.

These studies led Ehrlich to a thorough investigation of trypanosome infections. These resulted in the examination of the benzopurpurin series of drugs, which led him to trypan red and other compounds, and finally

to the arsenical drugs. He laid particular emphasis on the chemical combinations of the drugs with the parasite, as against their effect upon the tissues of the host.

The concept of chemotherapy developed by Ehrlich, as mentioned above, was made possible only through the property of certain chemical substances to act selectively upon different living cells. Ehrlich's preliminary work on the effectiveness of atoxyl as a chemotherapeutic agent led directly to his discovery of salvarsan, the "magic bullet." This was the first true chemotherapeutic agent that came out of a chemical or biological laboratory. It opened a new field in the treatment of human diseases. In introducing this drug into practical therapy, Ehrlich laid great emphasis upon the curative dose vs. the tolerated dose. He finally came to recognize the importance of the "therapia sterilisans magna," or the single shot treatment of infections.

The careless use of salvarsan by many doctors resulted in a number of serious reactions which were often blamed on Ehrlich and upon his discovery. I well recall how one day in 1918 a practicing doctor from a small town in North Jersey came to see me to inquire whether I would be willing to instruct him in the manner of treating syphilitic patients with this drug. On arriving at the agreed time, at the Doctor's office, I found in the chair a bulky fellow, a chauffeur by profession, who had just returned from Europe where he had contracted the disease. I brought with me a sample of the salvarsan manufactured by the company with which I was associated and demonstrated to the doctor and to several of his colleagues, assembled for this occasion, how to prepare the solution of the drug, how to neutralize it, how to find the vein in the arm of the patient. Following my instructions, the doctor made the injection. The patient got up, feeling quite well, and left the office, after being told to return in a week for a second injection. A few months later, I walked again through one of the main streets of that town. I was suddenly accosted by a thin emaciated man, a mere shadow of the patient whom I saw in the chair a few months earlier. He exclaimed: "You are the one man for whom I have been looking these past few months." He then proceeded to tell me that after he was given the second injection, he had to be carried out of the office on a stretcher. Upon leaving the hospital two or three months later, he had decided to determine just what happened to him. He was, therefore, on the constant lookout for me, since he knew that I was the only one who could tell him what was wrong with the manner in which he was given the second treatment. It

took me some time to establish the fact that the doctor had added to the salvarsan a great excess of a highly concentrated solution of sodium hydroxide, which was then injected into the patient's vein. I could, of course, hardly be a witness to the negligence of the doctor.

Ehrlich had to pay dearly, both in time and energy, in order to have the medical profession follow the detailed instructions concerning the use of salvarsan (No. 606). He fully recognized the need for observing in minutest detail the various precautions required in the use of this drug. He emphasized particularly the danger in using contaminated water. When news reached him of cases of deafness and neural relapses resulting from the use of salvarsan, he was much upset. He took it upon himself to instruct the doctors in its proper use. When he discovered neosalvarsan (No. 914), some of the difficulties experienced in the use of salvarsan tended to be overcome.

We have heard recently much discussion of the importance of "chance" vs. "systematic investigations" in scientific discoveries. Ehrlich's work had left little to chance. He was a great believer in teamwork, which has played such an important part in the recent discoveries of antibiotics. He expresses this as follows: "Centralization of investigation with independence of the individual worker." He was a great believer in the careful planning of research. However, the individual experiments were constantly modified as work progressed. He did not appear to attach much importance to the differentiation between "pure" and "applied research."

Unexpected observations were made great use of in the solution of given problems. It so happened that the kitchen maid forgot to remove the slides with his stained preparations of the tuberculosis organism from the stove. This led Ehrlich to recognize the importance of heating slides in making certain stains. But it was his systematic, unfailing, driving power, and faith in finding in time the right answer that produced his greatest discoveries. When one of his assistants tested in 1908 the effect of 606 in experimental syphilis and reported negative results, Ehrlich was convinced that something was wrong. Next year, in 1909, when the Japanese investigator Hata came to his laboratory, he was instructed to test this preparation very carefully. Positive results were now obtained thus confirming fully Ehrlich's expectations.

Paul Ehrlich represented the true scientist who does not sit idly by in deep contemplation waiting until a chance will come his way, but who searches information in every branch of science that can only

elucidate his particular problem. In his case, he devoted time and energy to cell respiration, to the action of dyes, to problems of immunity, to the nature of malignant growths, and to the selective action of chemical agents.

Following the discovery of salvarsan, honors began to pour in on Ehrlich including the Nobel prize which he shared with Metchnikov. When his 60th anniversary was celebrated in 1914, there came to him congratulations from all over the world and numerous distinctions from his own and other governments. The expression of gratitude of patients cured by salvarsan only partly tended to balance the abuse heaped upon him by some of the physicians who were hostile to its use. The outbreak of the First World War came as a final shock to him which finally led him to his early grave.

Ehrlich was a modest man. He was an optimist. He struggled his whole life for the advance of human health and the eradication of disease. He had a hasty temperament, but he was also very kind. It was said of him that "he could be loved as a child." The British bacteriologist Bulloch spoke of him as the "most extraordinary man I ever met; with his wonderful inspiration, his enormous power of work, his astonishing knowledge, he was the greatest man in the medical world of his time. He was modest, sincere, noble-minded, and with the greatest kindness and consideration towards everybody."

His own countryman, another great scientist whose life and work had in some respects a certain similarity to that of Ehrlich, Richard Willstätter wrote down his impressions of Ehrlich, when he came to Frankfurt, on March 14, 1914, to participate in the celebration of Ehrlich's 60th birthday. I am translating rather freely: "Ehrlich was a simple, basically good man, whenever he only had time for it. He concentrated entirely upon his indefatigable work, which drove him constantly from one experiment to another. His creative phantasy was always at work preparing him for new working hypotheses. His great capacity combined imagination with experiment. His persistence assured its success. Without being a chemist by training, he had the most unique experience in establishing the reactions of dyes in the broadest possible sense. His working cabinet, as well as his laboratory, was small. Each table and each chair was covered with books, reprints, memoranda, flasks and tubes of every possible form, and cigar boxes. The latter contained either imported cigars or tubes containing various chemical preparations. He knew and could find everything that was

there, even if it took a long time to look for it. His knowledge in his selected field was extensive and profound, although also one-sided. He could hardly afford the time to accumulate knowledge which would not serve to advance his own selected field for science."

Miss Marquardt, his secretary, describes him as follows:

"Ehrlich's manner was friendly and jovial to all around him, his fellow-workers, assistants and employees. New-comers, or people whose work did not often bring them in contact with the Chief, were, however, often a little embarrassed and uneasy when they had to see him, in spite of his amiability. This was partly because Ehrlich's exuberant manner made it hard to grasp his meaning at first, and his directions were always given with suggestions and allusions only. Also there was a little imp in him which made him make joking remarks with an absolutely serious face, and this, with his habit of making fun of himself, confused some people who were not used to it. Those who knew him well, however, could always guess what he wanted from the slightest hint.

"Ehrlich judged his fellow-workers and employees entirely by their knowledge and ability and the work actually done, and often thought it right to ignore weak points of character. He said that the private life of those who worked with him did not concern him providing they did their duty well, and he never listened to gossip or scandal."

Ehrlich neglected his health completely. All who knew him commented on his endless work, continuous smoking, and his irregularity of eating. He was indifferent to the comforts of life. He was generous to his assistants. He was very careful to give them full credit for their work. Among his most outstanding collaborators, one need only mention Morgenroth, Neiszer, Sachs, Shiga and Hata.

Need I emphasize again the fact that Ehrlich's work had a profound influence upon the development of microbiology as a whole and upon chemotherapy in particular. Humanity is greatly indebted to Ehrlich. Together with Louis Pasteur, Robert Koch and Elie Metchnikov, Paul Ehrlich has laid the foundation for modern therapeutic war on human and animal diseases. At a time when so much energy is being spent for the machines of destruction, the contributions of Paul Ehrlich and others who have followed in his footsteps have served the purpose of the saving of human life and of making this world a better and healthier place to live in.

PAUL EHRLICH AND MODERN CHEMOTHERAPY

Perrin H. Long

Generally, in the science of medicine, great discoveries or great advances in this field represent an accumulation of experiences that had been shared in by many investigators. However, this cannot be said to be the case in respect to chemotherapy, because time and the man Ehrlich came uniquely together in this instance to open and develop this branch of medicine. To be sure, chemotherapy had existed, probably from prehistoric times, because when man first ingested or rubbed on an elemental remedy for his illness, chemotherapy was born. We know that through historic times, when elements as simple as gold, quicksilver or antimony were used in the treatment of disease, that the physician was practicing chemotherapy, and interestingly enough, certain far-reaching observations, such as the value of mercury in the treatment of syphilis were made on an empirical basis.

It was said above, that in Ehrlich, the time and the man came together in a unique fashion. This should not be difficult to understand if one remembers that Paul Ehrlich was born in 1854, just two years before Pasteur began his monumental studies on fermentation and the diseases of grapes, work which opened and established the field of bacteriology. Thus during Ehrlich's boyhood and student days, Pasteur, Koch and other investigators were successively isolating and identifying first one, and then another, of the microbial agents which produce infectious diseases. It was in this era of intellectual and scientific ferment in medicine, that Ehrlich entered into his chosen career of medicine. From the beginning of his student life Ehrlich was not "run-of-the-mine." From the day he first looked through a microscope at a bit of stained tissue, he began experimenting with dyes to obtain better stains. He was never easily satisfied, and while he pursued his interests assiduously, he was not what one would call a brilliant medical student because in much of the curriculum there was little that interested him so he rejected it and in a sense just "got by." In 1878 he passed his licensing examination and moved directly into his beloved field of the staining properties of

various dyes on dead and living tissues, work which laid the very basis for our knowledge of the formed elements of the blood, the chemical reactions of various tissues, and which prepared Ehrlich for his major contributions in chemotherapy some twenty-five years later. Space does not permit a discussion of his work under Koch's aegis during which Ehrlich formulated his provocative and ingenious theory of cellular "side chains" as being basic in the production of immunity or resistance to infections and certain toxic processes. Suffice it to say that his studies of dyes, of blood, of immunity were sequential in directing his interests into the broad field of the chemical treatment of disease.

In 1902 Ehrlich's intensive work on chemotherapy began. First, because of interest and practicability, he studied the use of dyes in treating animals infected with the parasite of African sleeping sickness. Within a period of two years, he found that one of his early and favorite dyes, trypan red, would prevent or cure the experimental disease produced by one type of these parasites, but against other types this dye and other dyes which were tested were ineffective. He further noted that under certain conditions the parasites became highly resistant to the chemotherapeutic effects of the dye thus demonstrating drug resistance for the first time.

This led him to an investigation of other chemical substances, and one of the first to be used was an arsenical compound, called atoxyl. This would cure the experimental disease in animals, but when drug and parasites were placed together in a test tube nothing happened. To Ehrlich's inquiring mind this had to be explained and he soon found the reason, namely, that in the animal body the drug was changed to a compound which was highly active and quite different from the original substance.

It was known at that time that certain arsenical compounds had some curative activity against infections produced by a group of corkscrew shaped microbes. A few years before this time two German scientists had demonstrated that one species of this group of spiral organisms was the cause of syphilis. With this knowledge and with that of the new arsenical products which he was synthesizing, Paul Ehrlich went directly to the core of the matter and in 1910 produced an arsenical compound which he named salvarsan, and which became immediately, because of its potent favorable effects, the best remedy for treating syphilis and remained so until the curative effects of penicillin were demonstrated in this disease. Thus the science of chemotherapy was born, and curi-

ously enough, remained almost stationary for twenty years – or until the discovery of the sulfa drugs. Paul Ehrlich died in 1915, just five years after his genius had produced the first great chemical remedy for disease.

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SECTION ON MICROBIOLOGY

TUESDAY EVENING, NOVEMBER 27, 1951, AT 8:30 O'CLOCK

Induction of Penicillin Resistance by Transformation

ROLLIN D. HOTCHKISS

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The process known in bacteriology as transformation has been demonstrated chiefly by the induction of heritable modifications in certain species-specific or type-specific antigens.[1-6] In each case, desoxyribonucleic acid-containing extracts of a donor strain of bacteria conferred some of the heritable properties of this strain upon a recipient strain when the latter was grown in the presence of the more or less purified extract.

We have successfully transferred resistance to penicillin in pneumococci by procedures analogous to those of capsular type-transformation.[7] Penicillin-sensitive rough strain (R) organisms give rise to a proportion of penicillin-resistant (P) variants when grown in the presence of the desoxyribonucleic acid prepared from rough strains selected for spontaneously arising penicillin resistance. The yield of P transformants appears to be ten or more times greater

than the yield of Type III encapsulated organisms produced when a duplicate culture is exposed to the nucleic acid fraction derived from the usual Type III encapsulated ("smooth"; S) strains of pneumococcus. For example, a culture containing a million R organisms in one ml. gave rise to 24,000 P cells, and to only 1000 S cells, when exposed to 1.3 μg of the respective nucleic acid preparations.

Like other pneumococcal transforming factors,[7] the active principle in the R to P transformation is inactivated rapidly by exposure to crystalline pancreas desoxyribonuclease.[8] The biological activity of the preparations remains after proteins are removed by surface denaturation and alcohol precipitation, and after ribonucleic acid is destroyed by addition of ribonuclease. Selection of P transformants is made, not with anti-R-pneumococcus antibodies, but by addition of penicillin at an appropriate time, whereupon the untransformed population (the total population if the nucleic acid factor has been omitted or inactivated) are killed, spontaneously autolyze, and disappear. Any newly formed penicillin resistant cells remain and can be counted.

When penicillin resistant smooth (i.e., SP) organisms are the source of the desoxyribonucleic acid fraction, R organisms are converted to both the S and RP states but only a very low yield of SP ("double") transformants is produced. Transformations with respect to the S and P characters have apparently occurred independently, presumably as a reflection of the separate existence of two independently functioning desoxyribonucleic acid units in the transforming preparations used.

Resistance to penicillin appears to be acquired in discrete quantitative steps. The spontaneously derived and selected strains used in this work had become sufficiently resistant to grow in 0.30-0.45 units per ml. of crystalline benzylpenicillin. If a subscript is used to designate the upper limit in units of penicillin per 100 ml. at which a strain will grow normally, these strains are conservatively described as RP_{30} and SP_{30}. When a penicillin sensitive R strain (i.e., only resistant to the RP_1 level) is transformed with the desoxyribonucleic acid from either the RP_{30} or the SP_{30} strain, the first resistance level reached is rather uniformly an RP_8. Single colony strains from the RP_8 population when used as the recipient strain will however be converted in part to RP_{12} in a second exposure to the same RP_{30} or SP_{30} nucleic acids. Following this, RP_{12} strains can be carried at least one step higher to RP_{24} by the same preparations. Here too, then, a number of discrete transforming agents appear to be present in the single preparation, acting independently, and in this case in a particular sequence.

These steps of transformation appear to recapitulate the experience of the donor strain in originally acquiring spontaneously its resistance to penicillin, in agreement with the discrete mutational steps observed by Demerec[9] with staphylococcus. Such findings strengthen the view that transformation with specific desoxyribonucleic acids can accomplish changes that are considered to be true bacterial mutations. It should be pointed out that the donor strains used in these experiments remained resistant to penicillin during several months of routine passage without further exposure to this antibiotic. Penicillin has never been added to the recipient strain, until the time when it is used, after transformation is completed, to select for the newly produced resistant population.

An interesting new experimental approach to transformation has been made by treating mixtures of sensitive and resistant strains of pneumococcus with penicillin. The sensitive strains are sterilized and undergo lysis, whereupon active agents are released which are able to induce transformations in the surviving resistant strain. By such lysate-induced transformation, the synthesis of Type III capsular polysaccharide has been transferred from a Type III encapsulated, penicillin sensitive (SP_1) to Type II rough, penicillin resistant (RP_{30} or RP_{12}) pneumococci. The newly produced strain is a highly penicillin resistant, smooth Type III pneumococcus; so it may be concluded that in this "lysis transformation" the single Type III factor has passed over to the rough cells bearing the multiple penicillin factors.

A Type III smooth, streptomycin resistant pneumococcal strain was also used in lysis transformations. This doubly marked strain, SP,Stm, was developed by Miss Esther Weiss, whose valuable help throughout this work is gratefully acknowledged. When lysed with penicillin in the presence of the rough, penicillin resistant strain, the latter acquired independently of each other the two factors, capsular Type III and streptomycin resistance. This indicates that in a penicillin lysate, as well as in a desoxyribonucleate extract, the transforming agents can exist in part at least as independent units. Further evidence that the mechanism of lysis transformation is analogous to classical transformation in pneumococcus is furnished by the failure to obtain lysis transformation in all cases when a small amount of crystalline desoxyribonuclease is present. These latter experiments also provide adequate controls to rule out the possibility that spontaneous mutation can account for the production of the new strains. In addition they indicate that in these unfractionated lysates proteins or ribonucleates are not present in a form capable of actively inducing the same inheritable changes as the desoxyribonucleates.

Such transfer of inheritable properties from one population, undergoing death and lysis under the influence of a natural antibacterial agent, to another population surviving this influence, suggests that transformation may occur in nature. It could be expected to have evolutionary significance if, in response to certain environmental hazards, mixed microbial populations in nature on occasion preserve certain inheritable characters by transfer to surviving cells, with the possibility thereby of creating new species.

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Purification and Analysis of the Transforming Principle of Hemophilus Influenzae *

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The main non-dialyzable components of the crude transforming principles are the desoxypentose nucleic acid (DNA), the pentose nucleic acid (PNA), the proteins and the polysaccharides. While the transforming activity disappears with the removal or destruction of the first component, the DNA, this activity remains unchanged with the removal or destruction of the other mentioned compounds; for this and other reasons the DNA is regarded as the transforming agent[1] whereas the PNA, the proteins and the polysaccharides—as impurities. Of these, the proteins can be removed without difficulties.[1-3] The immunologically active polysaccharies have been removed only in a few cases;[1-2] the degree of removal of PNA has not been well described.

The method presented here permits the purification of DNA in general and the transforming principles in particular, by the removal of PNA, polysaccharides and possibly other not highly negatively charged impurities. It is based on observation that the DNA has an electrophoretic mobility higher not only than the serologically active polysaccharides but also sufficiently higher than the PNA of the same source to permit electrophoretic separation.[4] It will be described on the example of purification of transforming principle of *Hemophilus influenzae* type b and c.[5, 6]

Hemophilus influenzae type b and c was grown on Levinthal agar plates, harvested, lysed with sodium desoxycholate, freed of proteins by treatments with chloroform-octanol mixture, and precipitated by addition of ethanol, essentially as described by Alexander and Leidy.[5] The total precipitate was redissolved in 0.02 M phosphate buffer (containing 0.15 M NaCl) of pH 7.25. This solution containing 1.4 mg. DNA per cc., 2.3 mg. PNA per cc. and more than 0.5 mg. polysaccharides per cc. was subjected to electrophoretic separation in the Tiselius cell at 1.5°. Under these conditions the ascending mobility of DNA (very sharp peak) was -17.0×10^{-5} sq. cm. per volt per sec, and PNA -12.3×10^{-5}. Due to the high mobility and low diffusibility of DNA, it could be separated from PNA and other contaminants of lower mobility.

The DNA fraction contained less than 2.5 per cent of protein, less than 1 per cent of PNA and less than 0.2 per cent of the serologically active polysaccharides (referred to the DNA content). When dialyzed and dried (type c) it was found to contain 97 per cent DNA (N 15.75 per cent, P. 8.85 per cent, N/P 1.78). These results suggest that no major impurities are present in the electrophoretically separated DNA fraction. When this fraction from type c was analyzed for individual purines and pyrimidines, the following ratios were found: adenine/guanine = 1.76; thymine/cytosine = 1.47 (recovery over 94 per cent). These ratios are specific for the species *Hemophilus influenzae*.

The DNA fractions were active as transforming agents in the concentrations less than 0.01 gamma DNA per cc. for type c and less than 0.0004 gamma DNA per cc. for type b. The gradual removal of impurities resulted in an increase, rather than decrease of activity. These results suggest that the transforming principle of *Hemophilus influenzae* is not a protein, or a pentose nucleic acid, or a polysaccharide, but rather a highly polymerized desoxypentose nucleic acid.

* Work done in collaboration with Hattie E. Alexander, Grace Leidy, Patricia L. Fitzgerald and Erwin Chargaff.

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Transformation Reactions in Hemophilus Influenzae

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These investigations are related to the nature of the process which brings about a change in the inheritance of *H. influenzae*.

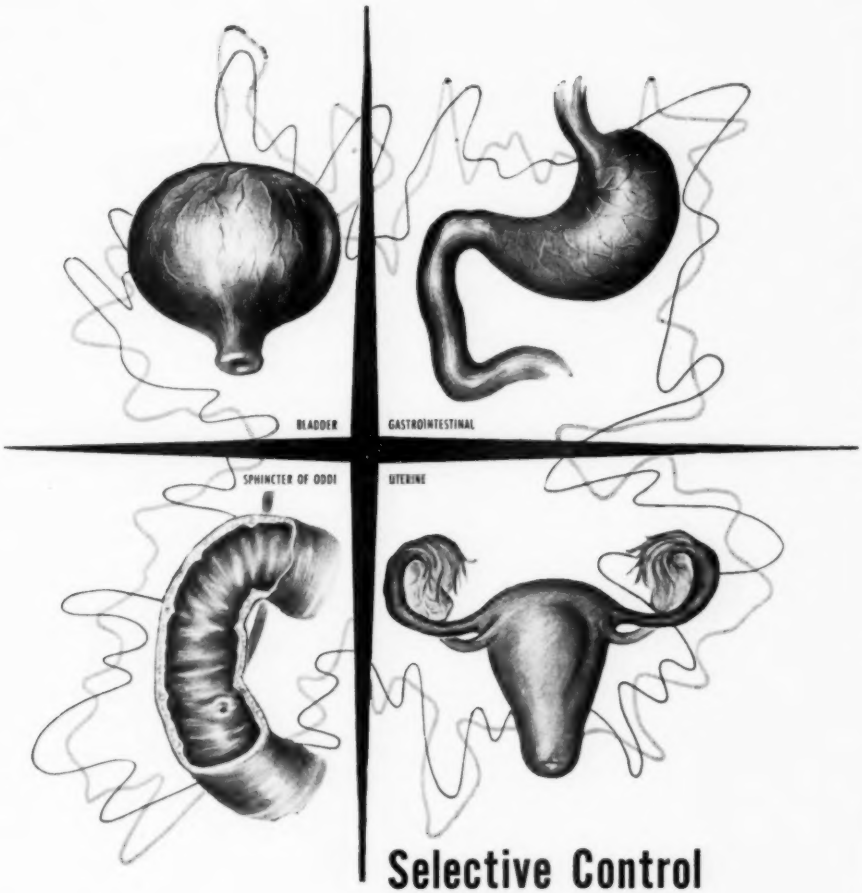
General Nature of the Process: The data are consistent with the hypothesis that the action of desoxyribonucleic acid containing extracts which change the inherited characteristics of this organism is not unlike other chemical reactions between two reagents. When both reagents, the desoxyribonucleic acid and the susceptible cells, are present the results permit the following conclusions: 1) The reaction takes place virtually instantaneously. 2) The process is apparently complete in less than 15 minutes. 3) Growth of the cells and anti-R antiserum are not essential for the reaction.

Nature of the Susceptible Cell: The results of investigations on the nature of the susceptible cell are consistent with the following conclusions:

A. Relationship of the susceptible cell to the rest of population. The susceptible cells make up only a minute proportion of the total population; they exhibit the following traits which are characteristic of mutants.
   1) The pattern of frequency of occurrence is consistent with this concept; this pattern depends upon the specific type from which the R cell is derived, is a constant trait and is heritable.
   2) The susceptible cell varies in its prevalence in different independent cultures of the same strain and population size.
   3) One essential trait of a mutant is inheritance of the mutant trait; this has not yet been demonstrated.

B. Influence of the type specific trait on susceptibility to transformation.

It has not been possible to show that either absence or abnormality of the type specific trait is a requirement for heterologous transformation. A new type can be induced with predictable regularity in a fully equipped type specific population derived directly from a single clone. No significant difference could be demonstrated between the rate of occurrence of susceptible cells in S populations of a given type and R cells derived from that type.



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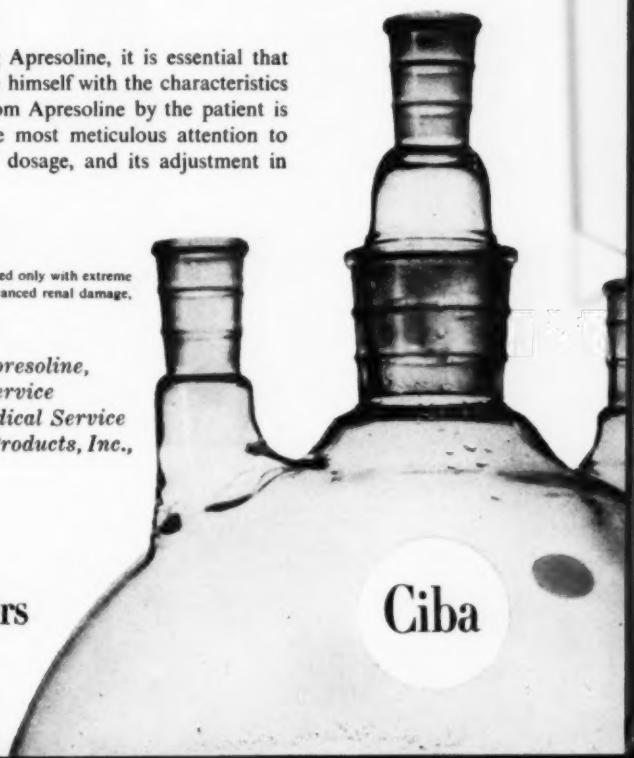

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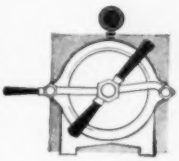

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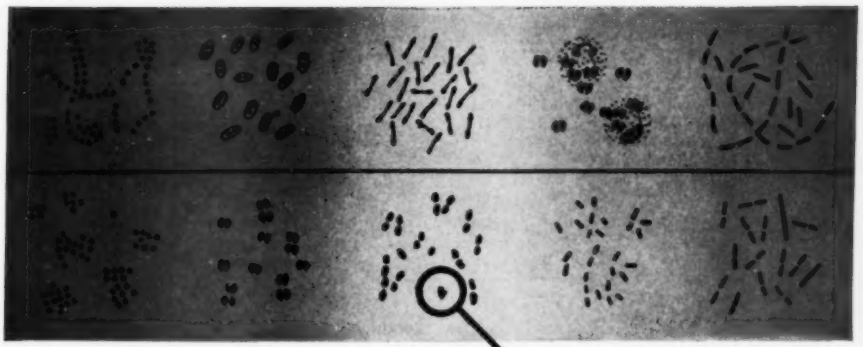

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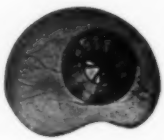

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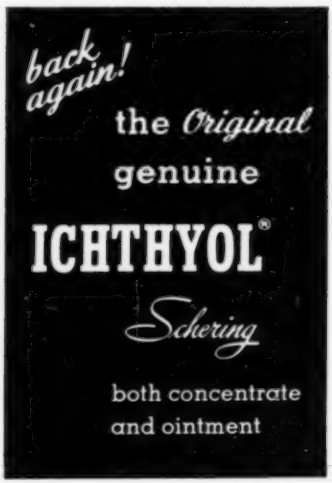

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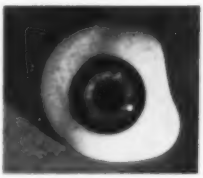

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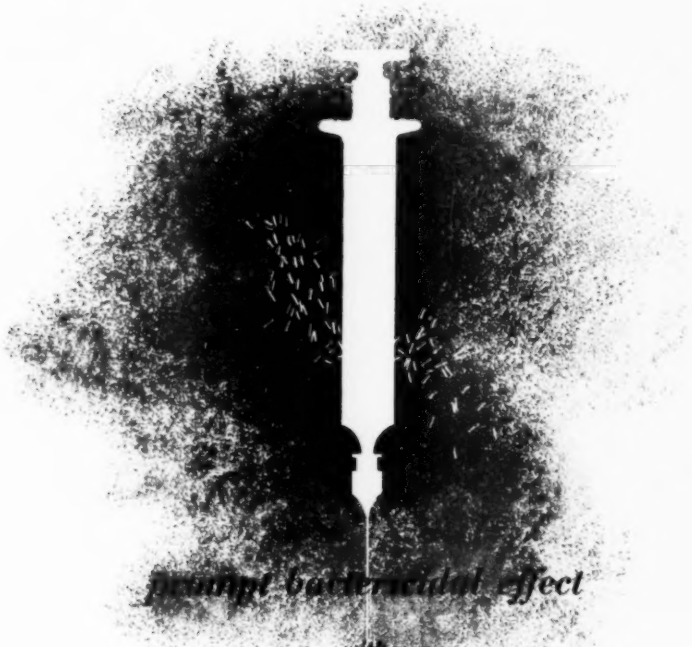

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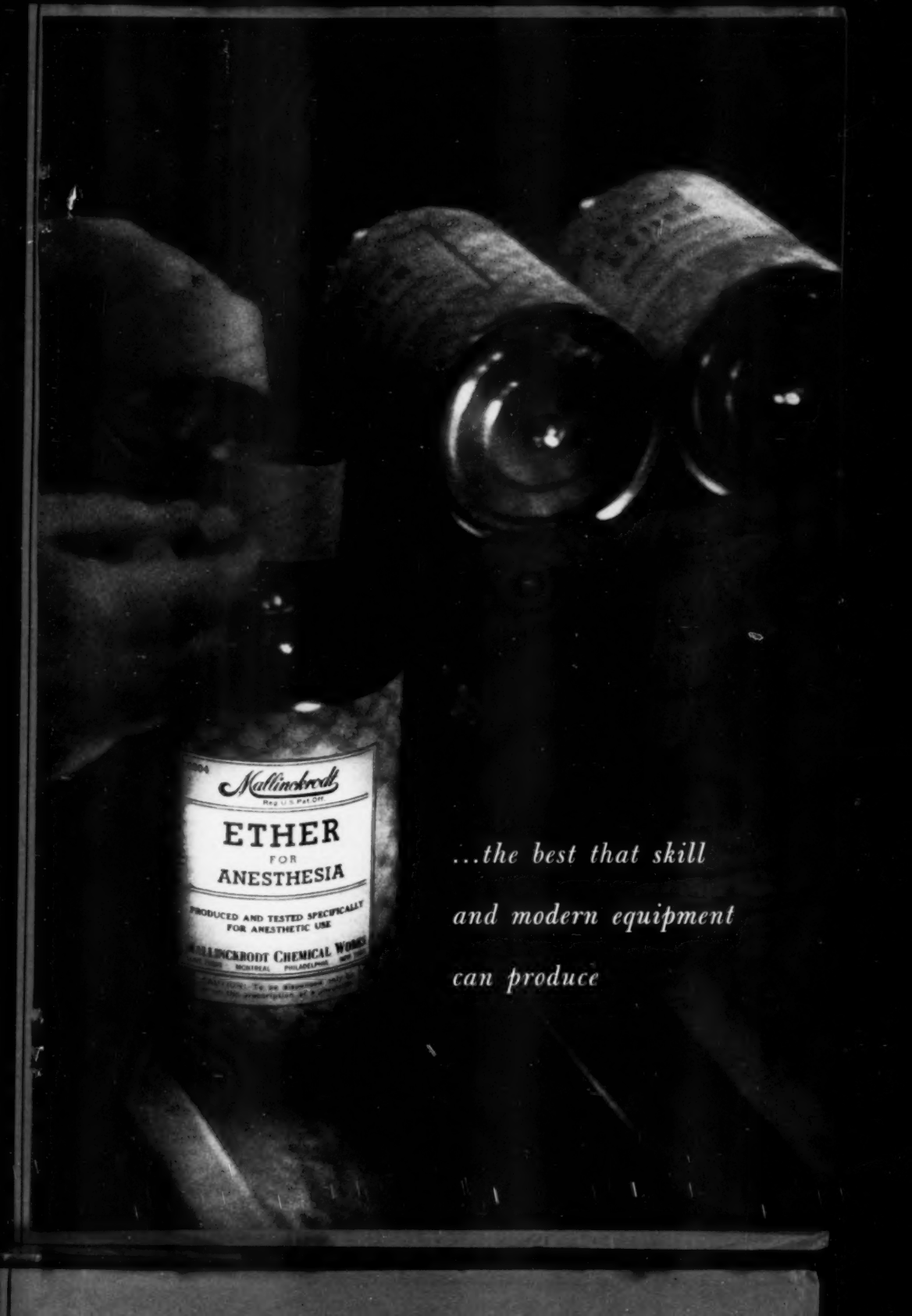
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bibliography: †Stromme, W. B., and Rothnem, M. S.: Clinical Experience with a New Gel-Alone Method of Contraception. World Population Problems and Birth Control, Annals of New York Academy of Sciences, Vol. 54, Art. 5, in press.

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